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"MIGRAINE, A STUDY OF ENVIRONMENTAL AND INTRAPERSONAL FACTORS"

by

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# "MIGRAINE, A STUDY OF ENVIRONMENTAL AND INTRAPERSONAL FACTORS"

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## SUMMARY

A study was carried out of 45 migrainous patients with visually induced migraine (VIM), and 25 migrainous students, each having an age and sex matched control. The study utilised questionnaires, interviews, electroencephalography (EEG) and visual evoked potentials (VEP). The experimental work and analysis was carried out in the Neuropsychology Unit in collaboration with the Birmingham Migraine Clinic, over a period of five years.

The study suggests:

1. The literature on a possible relationship between migraine and epilepsy hitherto published is unreliable (supporting evidence is given).
2. That a much greater precision is needed in defining migraine for research purposes.
3. A revised methodology for the selection of controls is needed and this is proposed.
4. That despite what are now seen to be superficial similarities, there are clear distinctions of a fundamental nature between photo-sensitive epilepsy (PSE) and VIM.
5. Caution be used when taking headache as a symptom, since many of the precipitants of migrainous headache can also precipitate non-migrainous headache (NMH).
6. The list of visual precipitants of migraine is expanded (particularly flicker and pattern).
7. That colour (principally red) is a previously unreported precipitant of migraine.
8. The extended range of responses to flicker (the 'H' response) has no significant difference in its frequency of occurrence in patients and normal controls, which contradicts previous literature.
9. The mechanisms thought to underlie migraine serve to explain previously unexplained EEG findings.
10. Further research is needed and proposed.

Key words: Migraine, Epilepsy, Photosensitive Epilepsy (PSE), Electroencephalography (EEG), Intermittent Photic Stimulation (IPS).

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The study would not have been possible without either the Headache Questionnaire developed by Prof. Waters of Southampton University, and used with his permission, or the active co-operation of the Registry Division of the University and of the staff of the Migraine Clinic. Needless to say, the study would also not have been possible

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Despite the contribution of so many, the views expressed in this thesis are the responsibility of the author.

\*\*

As from 1st August, 1978 Dr. Harding has become Prof. Harding, having been appointed to the second chair in the Ophthalmic Optics Department, University of Aston in Birmingham.

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SECTION I

LITERATURE REVIEW

## 1.1 The problem and the historical setting

### 1.1.1 An individual's experience of migraine and visual factors that trigger attacks

To non-sufferers migraine may be regarded as "just another headache" but an individual living through an attack would not agree. The following quotation from West (1975) is a personal account of his migraine attacks and well illustrates this.

"We subjects ..... dosed with painkillers or ergotamine tartrate, supine in dark rooms or sitting it out in sunglasses, we have not only a headache but nausea, a private firework display, and a paradoxical euphoria as well (some, such as my mother, have bouts that last several days, in the course of which they tend to vomit).

No wonder that migrainees feel a bond of sympathy with epileptics, hysterics, and spastics; but our sense of being out-of-control, while being also undistortedly aware of the fact from moment to moment, is one thing they do not share. In ambivalent experience, we come closer to sufferers from Parkinson's disease or Huntingdon's chorea, and often (as sometimes before a menu whose print swarms and veers, or trying to obey a traffic light whose colours combine) look just as unfit. Our lives are Moebius strips: the outside becomes the inside without much warning, and any slight tilt in the customary sensations - an enhanced relish, a quickening in repartee, a minimal intuition of something extra-sensory - can herald the roller-coaster, wall-of-death vertigo of a full-blown attack: one's visual field turns into a moire effect of watered or wavy patterns which are the spectrum scrambled (usually minus its greens) in slow motion, though with certain brilliant nodes of light erupting like tiny supernovae within the overall scheme. When I saw the spectacular light-show in Stanley Kubrick's film 2001, with astronaut Bowman hurtling through canyons of explosive, irregular colour, I felt on familiar ground, or at least in home aether, and for thirty seconds or so quite ignored the chance of the display's triggering an attack (as a strobe light can), such is the visual cortex's vulnerability.

..... I could almost guarantee an attack by staring at sunlit snow or brightly-lit white paper (hazards while sledding or reading!) In later years, the ballistically perfect, unrelievedly dazzling walls of a squash court had much the same effect, so I played the game in dark glasses.....

Sufficient to say, one lives as prudently as one can, careful not to lock gazes with flashbulbs, headlights, or television's lamps, and to be on special guard against the brute magnesium spot that is sunlight bull's-eyed on the chrome trim of a car: a photon-punch whose after-effect swells in just a few minutes from a retinal black hole into a band of brightness that spreads across one's vision like the charring scar on a newspaper held against the fireplace to increase the draught. Soon the paper blazes up of course, whereas the eyes blank out in a spherical funk in which not even banner headlines can be read."



### 1.1.2 The general aims of the study

The above quotation is superbly descriptive and illustrates well the complexity of the problem and the unsubstantiated hypotheses relating migraine to other afflictions. It emphasises the importance of visual triggers and these necessarily form a major aspect in this study of migraine. Consideration will also be given to photosensitive epilepsy. The great danger of this study is that the aims shall be too generalized and yet there is a great need for unification of the research material available. A conflict of aims which necessarily pervades the whole of this study, is thus evident.

It was decided to examine the literature under the following headings

1. Current definitions and diagnostic criteria for migraine.
2. The underlying reasons for the variation in the estimates of the prevalence of migraine in the population.
3. The factors which may trigger migraine, with particular emphasis on visual factors; what proportions of the migrainous are thought to be affected by them.
4. Current thinking on the mechanisms underlying migraine and whether precipitation by visual factors is explicable in terms of these.
5. Thinking on a possible relationship between migraine and epilepsy.
6. Precipitants of photosensitive epilepsy and its electro-encephalographic and evoked potential characteristics.
7. Electroencephalographic and evoked potential findings in migraine.

### 1.1.3 Historical setting

When examining the literature, one of the recurring themes has been the suggestion of possible relationship between migraine and epilepsy. It is relevant to ask whether this arose as a matter of hearsay or of sound observation. Authors quoting from ancient literature suggest migraine was reported as long ago as 5,000 B.C. and was studied by Hippocrates, Artaeus of Cappadocia and Galen. (Lennox and Lennox, 1960; Critchley, 1967; Hanington and Harper, 1968; Dalessio, 1969; Hall, 1971; Office of Health Economics, 1972; Hachinski, Porchawaka and Steele, 1975; Sacks, 1973; Friedman, 1975b). None of these early writers is credited with suggesting a link between migraine and epilepsy although both conditions were recognised. Arteus of Cappadocia (A.D. 50-90) being commonly regarded as the discoverer of migraine, since he isolated a group of headaches characterized by their paroxysmal nature, severity, one-sidedness, association with nausea and separated by intervals free of discomfort. It is, however, Galen (A.D. 151-201), who is credited with the introduction of the term "hemicrania" (the Greek word meaning half a skull), which by slight distortion became known as "megrim" or "migraine".

Not until the writings of Thomas Willis in the seventeenth century is the first hint of an association between migraine and epilepsy made. He was a pioneer clinical neurologist and set out to review the entire field of nervous disorders in his work "De Anima Brutorum", including a section "De Cephalagia" which may be regarded as the first modern treatise on migraine. The classical theories had held that migraine was peripheral in origin, arising in one or more of the viscera (the stomach, the uterus, etc.) from which it is propagated about the body

by a special form of internal visceral communication termed "sympathy" by the Greeks. Willis suggested sympathetic communication took the form of an infinitude of minute pathways about the body (inferred sympathetic nerves) and extended this concept not only to migraine but also to many other paroxysmal disorders. He revived the classical notion of diopathy, (a tendency to periodic and sudden explosions in the nervous system). He therefore suggested the "migrainous nervous system" or the "epileptic nervous system" could be detonated at any time by a variety of physical or emotional factors, the effect of the explosions being carried throughout the body by the inferred sympathetic nerves. As will be shown later, recent thinking has again returned to the contribution of the sympathetic division of the autonomic nervous system to migraine.

The first specific suggestions of a link between migraine and epilepsy are reported as being made by Edward Liveing in 1873 in his treatise "On Megrin, Sick-Headache, and Some Allied Disorders" which is regarded as the first major work devoted to migraine and is referred to by many subsequent authors. It was however Gowers who considered migraine as a form of epilepsy and the title of his book published in 1907 "Borderlands of Epilepsy" was borrowed by Lennox and Lennox (1960) for the chapter on migraine in their book "Epilepsy and Related Disorders". The influence of these later writings is such that more recent reports considering the relationship between migraine and epilepsy are contributed by those whose primary interest is in epilepsy as well as those with a primary interest in migraine.

The conclusions of Liveing and Gowers were based on observations of the similarities of certain clinical symptoms (see section 1.9). With the advent of electroencephalographic techniques came the opportunity to monitor abnormalities in brain functioning, and those characteristic of epilepsy have been identified and are referred to in section 1.9. Abnormalities reported in the electroencephalograms of migraine sufferers are dealt with in sections 1.9 and 1.10 and their contribution to the suggestion of a relationship between migraine and epilepsy discussed, as is their relevance to other theories on the mechanisms of migraine.

## 1.2 Defining migraine and other headaches and the problem of differential diagnosis

There are very few people who have never experienced any form of head pain but it should be borne in mind that a headache is merely a symptom and that there are a number of possible underlying causes which are not mutually exclusive, indeed it is not uncommon to find patients with both migraine and tension headaches occurring simultaneously (Pearce, 1975a; Blumenthal, 1969). It was therefore important to consider definitions of migraine for two major reasons. Firstly, so that when the literature was examined some assessment could be made as to whether the persons studied as 'migrainous' would fall within currently accepted criteria; secondly, so that when experimental and control subjects were selected for study they would be correctly allocated as migrainous and non-migrainous, although either group might suffer tension headaches, for example.

The different types of headache were classified by the widely quoted Ad Hoc Committee on Classification of Headache of the National Institute of Neurological Disease and Blindness, Bethesda, U.S.A. This classification of headache is given in full by both Friedman et al (1962) and Vinken and Bruyn (1969), while Lance (1973) gives a version modified by consolidation and rearrangement of some categories. The original version outlining fifteen groups of headache is given in Appendix 1.

The definition for "vascular headaches of the migraine type" given by Friedman et al (1962) was slightly altered when the following definitions were agreed at a meeting of the Research Group on Migraine and Headache of the World Federation of Neurology at its meeting in

London 1969. Critchley (1970) gives the full definition and it is also quoted by Lance (1973) and Pearce (1975a). The definition is quoted below in abridged form.

DEFINITION OF MIGRAINE (Critchley, 1970)

A familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting. In some cases they are preceded by, or associated with, neurological and mood disturbances.

All the above characteristics are not necessarily present in each attack or in each patient.

(A) Conditions generally accepted as falling within the above definition:

1. Classical migraine, in which headache is preceded or accompanied by transient focal neurological phenomena, e.g. visual, sensory or speech disturbances.
2. Non-classical migraine, which is not associated with sharply defined focal neurological disturbances. This is the more common variety encountered.

(B) Conditions which may fall within the category of migraine:

1. Cluster headaches. Unilateral intense pain involving the eye and head on one side usually associated with flushing, nasal congestion and lacrimation, attacks recurring one or more times daily and lasting for twenty to one hundred and twenty minutes. Such bouts commonly continue for weeks or months and are separated by remissions of months or years.

2. Facial "migraine". Unilateral episodic facial pain associated with symptoms suggestive either of migraine or cluster headache.
3. Ophthalmoplegic "migraine". Episodic migraine-like attacks associated with objective evidence of paresis of the extraocular muscles usually those supplied by the third nerve, often outlasting the headache. A structural abnormality must be excluded before this diagnosis is made.
4. "Hemiplegic migraine". A rare condition, which may exhibit a dominant inheritance, characterized by episodic migrainous attacks associated with hemiplegia outlasting the headache.

This is a useful classification and was used in this study. However it is not universally accepted. Lance (1975), for example, thinks cluster headache is a distinct entity from migraine and the debate on this issue continues (Ekblom, 1974; Sjaastad, 1976; Medina and Diamond, 1977).

The classification is also not completely comprehensive since the following conditions, which some authors would include, are not specifically included.

1. Abdominal migraine

The headache of migraine attacks is not the major symptom, instead a headache may or may not precede such gastro-intestinal symptoms as abdominal cramps, nausea, vomiting and diarrhea. Such attacks in children are sometimes termed bilious attacks and these patients often

develop the more typical symptoms later in life. Such children may also be unduly prone to travel sickness. While reported in patients of all ages abdominal migraine is most common in children.

(Catino, 1965; Carroll, 1968; Graham, 1969; Hall, 1971; Poley and Bhatia, 1973; Friedman, 1970, 1975b; Lundberg, 1975; Nightingale, 1976; Prensky, 1976). Some authors do not regard such manifestations as a migraine equivalent, including Lance (1973).

## 2. Ophthalmic migraine

This migraine equivalent is characterized by temporary visual disturbances including complete blindness, other scotoma, amblyopia hemianopsia or visual hallucinations which mark the height of an attack of migraine instead of acting as a prodrome to the headache. The various types of visual disturbance associated with migraine are described in section 1.1.3. One or both eyes may be affected, and if the disturbances are limited to one eye rather than one half field then the term retinal migraine may be employed. (Catino, 1965; Carroll, 1968; Riffenburgh, 1971; Lance, 1973).

## 3. Basilar artery migraine

This condition, which is also known as vertebro-basilar migraine, was first described by Bickerstaff in 1961 and is given as a migraine variant by Hall (1971); Golden and French (1975); Pearce (1975b); Nightingale (1976) and Prensky (1976). The symptoms include impairment of conjugate eye movements, visual disturbances, bilateral paraesthesiae and dysesthesiae, dysarthria, tinnitus, vertigo, ataxia and drowsiness or confusion which may culminate in unconsciousness. Occipital headache and vomiting generally follows these attacks which are thought to be caused by constriction of basilar and posterior cerebral arteries,



and the fainting to result from ischaemia of the reticular formation. Such attacks occur mainly in young people, especially adolescent girls. Pearce (1975b) makes the point that the attacks "can be mistaken for more serious structural lesions of the brain stem, particularly disseminated sclerosis, although in the latter conditions the symptoms are measured in days and weeks rather than in minutes".

#### 4. Other migraine variants

As with the other migraine variants these may or may not be associated with headache, when migraine sufferers have episodes of focal neurological disturbance without headache or vomiting these are called migraine equivalents. The first group listed below is often suggested as replacing in patients for a period of time migraine attacks with more generally accepted symptoms. These include pseudo-angina (Friedman, 1970); paroxysmal tachycardia (Carroll, 1968; Graham, 1969; Friedman, 1970, 1975b; Hall, 1971) and thoracic or precordial pain (Catino, 1965; Graham, 1969; Friedman, 1975b; Prensky, 1976), incidentally Leon-Sotomayor (1974) groups these together under the term cardiac migraine. Also included are paroxysmal attacks of vertigo (Graham, 1969; Friedman, 1970, 1975b; Prensky, 1976); in addition migraine headaches may occur in association with the symptoms of Meniere's disease, that is tinnitus, hearing loss and vertigo (Carroll, 1968); and furthermore McArdle (1969) distinguishes periodic aural neuralgia and facial migraine to which Carroll (1968), Bruyn (1969) and Sacks (1975) would add facioplegic migraine (an extremely rare form, with facial paralysis). Other paroxysmal disorders also occur in migraine patients and may represent migraine equivalents, although in some instances the justification is less evidenced or accepted. These additional disorders include clinical features of meningeal irritation

of abrupt onset and clinically indistinguishable from subarachnoid haemorrhage but with no evidence of bleeding on immediate cerebrospinal fluid examination, (Carroll, 1968; Pearce, 1975b); pain in the extremities (Friedman, 1975b; Prensky, 1976); cyclical edema (Friedman, 1970, 1975b); "recurrent pelvic pain" (Catino 1965; Graham, 1969; Friedman 1975b); interstitial cystitis (Graham, 1969); recurrent bouts of fever (Wolff, 1963; Graham, 1969; Friedman, 1975b; Prensky, 1976); recurrent skin lesions (Catino, 1965; Graham, 1969) and finally periodic psychic disturbances may predominate, these including confusion, lethargy, sleep disturbances, elation, depression and other mood and behaviour changes (Catino, 1965; Carroll, 1968; Graham, 1969; Friedman, 1975b).

From the preceding consideration of both the widely accepted types of migraine and various migraine equivalents, it may be appreciated that the presenting symptoms of an attack may mimic or closely resemble other conditions associated with headache, including vascular abnormalities, other space-occupying lesions, and sub-arachnoid haemorrhage. This situation is complicated further since migraine may occur in between, or at the same time as, headaches of a different type. When migraine equivalents occur without headache the task of differential diagnosis is made more difficult. The problem and clinical significance of differential diagnosis is discussed by many authors (Blumenthal, 1969; Heyck, 1969; Lyle, 1969; Friedman, 1970, 1975b; Hall, 1971; Lance, 1973; Patten, 1973; Poley, 1973; Sacks, 1973; Prensky, 1976).

### 1.3 Diagnostic criteria for research purposes

Pearce (1975a) drew attention to the need for precision in diagnostic criteria in order to obtain unambiguous diagnosis. On the one hand a too precise set of criteria may exclude many cases seen in clinical practice as being atypical, thus resulting in therapeutic neglect by "errors of omission". On the other hand scientific research requires rigid and precise criteria so that groups which may differ can be seen and compared, so preventing the inclusion in any one group of inappropriate subjects ("errors of commission"). In reading papers on migraine these two standpoints, at the extreme ends of a continuum need to be constantly borne in mind. Some workers may try to position themselves in the middle of the continuum, which serves only to increase confusion. In this work I have tried to remain at the scientific end of the continuum, while maintaining an attitude of sympathetic understanding of the clinical workers' operational problems, should they be nearer the other end of the continuum.

Many authors simply state that the patients studied were diagnosed clinically, and where the authors are describing cases with clinical manifestations of interest, or dealing with clinical practice this is of value. However, articles purporting to be research orientated may explicitly reject diagnostic criteria. Such a statement is made by Leviton et al (1974).

"A potential weakness of this study is the lack of operational definitions. Migraine was not defined by objective criteria because a widely accepted set of diagnostic criteria is not available" (p.671).

More often no apology is given nor any diagnostic criteria, although increasingly authors refer to one or other of the definitions considered in section 1.2.

Examples of the definitions and diagnostic criteria used will now be considered. Working in clinical practice Hay (1968) states that

"to diagnose migraine the patient must have headache, with either visual disturbance or nausea as the minimum requirements." (p.42).

However Barolin (1966) used far less specific criteria for migraine in his study considering a relationship between migraine and epilepsy, for he wrote

"A headache of high intensity having a sudden onset and end is diagnosed "migraine" ..... the frequent accompanying symptoms such as hemilateralisation, vomiting, eye symptoms, etc. will support our diagnosis but we do not consider them indispensable for the diagnosis (as some authors do)."

Barolin may thus have included in his group some people not usually considered migrainous.

Studies giving operational sets of criteria make replication of their studies not only possible but easier to do. Vahlquist (1955) gave one of the early operational sets of criteria and this was to form the basis of the more elaborate set used by Prensly (1976) which is quoted as an example.

"The headache must be recurrent and separated by symptom free intervals and be accompanied by at least three of the following six symptoms: abdominal pain, nausea or vomiting; localized unilateral headaches or hemicrania; a throbbing pulsatile quality to the pain; complete relief after a brief period of sleep; an aura which may be visual, sensory or motor; and a family history of migraine."

Two papers of particular relevance to this study are by Golla and Winter (1958) and Smyth and Winter (1964) for they investigated the electrophysiological response to flicker by migrainous subjects. Their criteria, as stated by Smyth and Winter (1964), were based on those of Dow and Whitty (1947) and were also given in operational form as follows.

"Paroxysmal recurrent headache, without demonstrable structural intracranial lesion, accompanied by three of the five following clinical features: a family history of similar headache; relief of headache by ergotamine; hemicranial distribution at some stage; association with nausea or vomiting; preceding symptoms of teichopsia, scotoma, hemianopia, paraesthesiae, monoplegic or hemiplegic weakness or dysphasia."

This set of criteria have the disadvantage, for research purposes, of including relief of headache by ergotamine. This is disadvantageous on two counts. On the one hand the scientific usefulness of this on practical grounds of being unreliable, and on the other hand on ethical grounds in that one should only give a drug of this kind if one is already convinced that the person is migrainous on the basis of the remaining criteria. Thus one should rule out testing with ergotamine for a diagnostic purpose and use it only therapeutically in those cases where the patient responds beneficially. (Waters, 1970b).

The actual criteria used in this study can be compared and contrasted with those considered above, by referring to section 2.1.1. entitled "Headache Questionnaire 1 (HQ1)" and section 2.2 entitled "Selection of subjects - the methods used". In the event only three satisfactory operational criteria emerged from the literature study, which were those used by Professor Waters and formed the basis of his questionnaire, which had the additional advantage of being a clinically validated postal questionnaire. This questionnaire was therefore used with confidence in this study as Headache Questionnaire 1 (HQ1), for preliminary selection of subjects. As will be shown later, while this confidence was justified in that it provided a good foundation for these studies it did not however meet the demands made upon it in this research, as will emerge in Sections 2.1 and 2.2.

#### 1.4 The Symptoms of Migraine

The use of Professor Waters' Questionnaire (HQ1) proved to be less than satisfactory for this investigation. It is not that it was wrong, for the criteria were excellent, but that the criteria needed refining and sub-dividing to suit the purposes underlying this work (see sections 2.1 and 2.2). An additional review of the literature in this section is undertaken to seek out these sub-divisions, at the same time the extra work was used for two additional purposes as follows:

(a) to crystallise out descriptions of migraine aura; (b) to uncover proposed mechanisms underlying the symptoms described for migraine, except that those for the headache will be dealt with in another section.

These three purposes are covered in detail in the review below and led amongst other things to the development of part of Headache Questionnaire 2 (HQ2), to be used in addition to HQ1, as described in section 2.1.2.

The following description of symptoms associated with migraine is intended to convey their range and is not an all inclusive inventory. It should be remembered that there are grad-ations of the migraine complaint from the most severe and disabling illness to trifling symptoms; that not all symptoms are likely to occur in any one attack and that an individual sufferer might never experience some of the symptoms although they may present with different types of attack on different occasions. The descriptions given below are condensed from those of Duke-Elder (1949); Walsh (1957); Lennox and Lennox (1960); Hay (1968); Bruyn (1969); Hay, (1971); Delassio (1972); Hanington (1973); Lance (1973); Sacks (1973) and Wakefield (1975) with other authors being quoted as appropriate.

#### 1.4.1 The warning signs, excluding classical aura

While there are no recognisable physical symptoms between attacks, sufferers may be subject to warning symptoms or prodromal features.

In the days before an attack weight gain and reduced urinary output are occasionally seen, often with associated constipation, particularly in pre-menstrual migraine, associated with swelling of fingers, waist or breasts and puffiness of face and eyelids, further into an attack there may be an increase in frequency or volume of urination. Dehydration may be aided by diarrhea or by vomiting in the final phase of the attack.

The day before an attack there may be mood disturbances (Graham, 1969). The sufferers may experience an unexplained sense of well-being with increased clarity of thought, and find themselves able to achieve more in a given time than usual, in some cases the sense of elation is euphoric; some individuals may feel socially disinhibited, excessively talkative and perhaps be reluctant to retire to bed; there may be feelings of mounting tension; these symptoms are often followed by profound sleep just preceding the headache.

Other people are aware of declining energy and drive, feelings of depression or agitation, and sometimes bouts of irresistible yawning accompany these. The individual may become extremely unsociable, very irritable and is often unwilling to assume responsibilities, especially rejecting any demand to make decisions. Judgement and intellectual functioning may become poor (Willanger, 1975) and actions impulsive and even hostile or destructive (Lee and Lance, 1977).

Besides these mood disturbances, pains in the neck and shoulders may be experienced and in many patients tension headache, with qualities different from migraine headache, may occur prior to the migraine attack and are related to worrying situations. Such tension headaches may merge imperceptibly into a full-blown migraine attack (Migraine Trust, 1976; Pearce, 1976).

#### 1.4.2 Transient symptoms of classical and complicated migraine

The transient neurological symptoms of classical migraine may occur independently of headache as a migraine equivalent (see section 1.2), but generally precede the headache phase, although they may overlap this, and are consequently termed aura or prodromes. The brief duration of these symptoms, reported as mainly visual disturbances, which usually last 20 to 40 minutes makes their study difficult.

Complicated migraine is regarded as a type of migraine associated with transient symptoms of excitation (mainly sensory) and/or transient or, rarely, permanent deficit (mainly motor but also sensory). These symptoms include visual field defects, disorders of visual, auditory and other types of perception, tinnitus, vertigo, partial or total paralysis and mental disturbances.

The use of the terms classical and complicated migraine show some overlap in the literature and might be regarded as a continuum since generally, the more severe the attack the greater the number of symptoms and the more severe those symptoms (Klee, 1975a, 1975b).



The underlying causes of migraine are discussed later, but it is helpful at this stage to mention that the neurological aura are conventionally related to intracerebral vasospasm of the appropriate section of the vascular system, and the resulting hypoxia and ischemia of the surrounding brain tissues.

The most commonly reported symptoms result from such disturbances in the visual cortex causing "spots before the eyes" and temporary blindness (partial or total). One unresolved question is whether visual disturbances are reported most often because they are the most frequently occurring symptoms or because patients, fearing the onset of eye disorders, blindness or a stroke, are more likely to consult their doctor about these rather than about the other types of perceptual disorder. The excitatory visual disturbances include photopsia (bright unformed flashes of light or colour), geometric designs, stars, circles, squares or wiggles. Most of these are mobile and interfere with vision. Particularly well-known is the scintillating scotoma, otherwise known as the fortification spectra or teichopsia. This is described in detail by several authors including Richards (1971), Riffenburgh (1971), Pöppel (1975), Elbom (1975) and Speer (1975). This starts as a small paracentral negative scotoma without light phenomenon and may easily be missed unless the person is reading. During the next few minutes the scotoma expands into a horseshoe or semicircular shape with bright zig-zag scintillating lines appearing at the outer edge. These lines are small at first, but grow as the blind area expands and moves outward towards the periphery of the visual field. Generally the blindness does not involve the complete visual field but occurs as a band of blindness immediately following the arc of scintillations.

Many people have suggested that the expanding arc represents a wave of excitation radiating from a single region of the cortex. Richards (1971) refers to the work of the neuropsychologist H. S. Lashley published in 1941. He estimated on the basis of his own scintillating scotomas a propagation rate of three millimetres per minute. Quoting from Richards (1971):-



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Besides the scintillating scotoma, the other excitatory visual disturbances described may also be followed by loss of vision, although in some cases scotomas develop without preceding excitatory disturbance being noted. These may take on geometric shapes or there may be total loss of vision, hemianopia, or more rarely altitudinal or quadratic defects (Hachinski et al, 1975). Rarely the defects of "bright spots" or "holes in vision" may occur monocularly, the suggestion being this represents trouble in the one retina or its nerve.

The above disturbances are usually distinguished from other visual difficulties such as hypersensitivity to light which may become photophobia; focusing difficulties; increased lacrimation and edema of

the lids; the ophthalmoplegic phenomena that can accompany the headache and may persist for some time afterwards; and the disorders of visual perception, which are considered below with other disorders of perception.

Symptoms of excitation or deficit also affect modalities other than vision, including tactile sensation, hearing and speech, perception, taste and smell. These modalities will now be considered. As regards tactile sensation, the body is represented on the anterior margin of the parietal lobes, and if this area of a parietal lobe is affected then the symptoms will be experienced on the opposite side of the body, especially the face, hand or arm. These symptoms are paraesthesia which may be followed by hypoalgesia or anaesthesia.

At the upper margin of the temporal lobe, is the auditory area and immediately in front of them is the vestibular area. Disturbances associated with these areas are hyperacusis and phonophobia, tinnitus, and giddiness or true vertigo. There are also other disorders of hearing and the perception of the spoken and written word, as well as disorders of speech, including dysphasia, aphasia, anomia and dysarthria.

The disorders of perception are seen as arising in the association areas of the cortex where information from the primary sensory areas is interpreted (Speer, 1975). These disorders of perception are considered in detail by Klee (1975a), Hachinski et al (1973) and Livesley (1973). The various disorders of perception are sometimes termed "The Alice in Wonderland Syndrome" since so many of them are aptly described by Lewis Carroll, himself a sufferer from classical or complicated migraine (Livesley, 1973).

The experience of "déjà vu" or "jamais vu" is thought to involve the temporal lobes, which are also implicated in a particular form of visual hallucination described by Pearce (1976).

"Occasionally visual hallucinations with highly integrated visual images produce the illusion of a person, object or animal, usually described in vivid primary colours. The more sophisticated the form, the more likely is the focus of ischaemia to be anteriorly placed in the temporal lobe or the temporo-occipital radiation."

The various visual disorders of perception include a shining ring following the outline of an object (corona phenomenon); distortions of shape (metamorphopsia, mosaic vision); distortions of size (micropsia, macropsia and zoom vision); distortions of position (including teleopsia when an object is perceived as being further away, inversion of objects, and optic alloesthesia when an object situated in one part of the visual field is experienced as lying in a different part); distortions of movement (smoothly moving objects experienced as moving jerkily, cinematographic vision and autokinesis); colour changes; positive after images; reduplication of objects once or several times (diplopia and polyopia) and finally asthenopic scotoma, which implies the disappearance of part or the whole of an object. Occasionally there is a rhythmic alteration in these changes, called pulsation, which Sacks (1973), when referring to cinematographic vision, suggests is at 6 to 12 per second.

Disorders of auditory perception are less well documented but among the experiences described are hyperacusis associated with an echo effect, speech perceived as too slow or jerky, and disembodied or "heavenly" voices heard. Other disorders associated with language are alexia, agraphia and various forms of aphasia. Willanger (1975) suggests aphasia is present in about 20% of incapacitated patients.

Other disorders include synaesthesia (when the experience of a sensation in one place is due to stimulation applied in another, as when sound produces a sensation of colour) and agnosia, that is the loss of power to recognize the import of sensory stimuli, as when the faces of relatives become briefly unrecognizable (prosopagnosia) (Pearce, 1976). There may also be spatial disorientation with right-left confusion (Hall, 1971), or disturbances in the perception of body image. It is relatively rare for people to undergo on the one hand, the experience that the whole body or various parts are felt to have changed in size and proportion or on the other hand, the experience of the body, or parts of it, as foreign, that is not belonging to oneself.

It is also thought there are disturbances of taste and smell (Hall, 1971; Klee, 1975a).

Mention should also be made of disorders of the hypothalamus (dilation of the pupils, rhinorrhea, salivation, hyperhidrosis and flushing), of the cerebellum (ataxia) and those of basilar artery migraine. The basilar artery supplies the brain stem, the internal ear, the cerebellum and posterior cerebrum with the symptoms being confusion or unconsciousness, tinnitus, vertigo and ataxia.

It is worth noting two factors. Firstly, that the disturbances of sensation and perception are usually experienced simultaneously with other neurological symptoms, e.g. photopsia, vegetative symptoms (especially vomiting and diarrhea), vertigo and disturbances of speech. Secondly, that the incidence of disorders of perception may be much underestimated, since sufferers are afraid to tell others about them

in case they are thought to be psychiatrically disturbed or hallucinogenic drug addicts.

Finally, in addition to disorders affecting musculature already mentioned, that is dysarthria, ataxia and the paralysis of the parts supplied by the oculomotor nerve in ophthalmoplegic migraine, patients may suffer hemiplegia or more usually hemiparesis, although occasionally only one limb is affected. The paralysis may last for only a short time and clear with the onset of headache, or at the other extreme, outlast the headache for days as normal functioning only gradually returns, in which case it is known as hemiplegic migraine.

The literature on migraine aura was surveyed to crystallise out descriptions of these aura and mention has been made of aura consistent with excitation of parts of the cortex or else reduced functioning of these parts thought to be attributable to vasoconstriction, ischemia and edema. It is of interest that electroencephalographic and evoked potential findings obtained during episodes of temporary loss of vision or temporary hemi-plegia yield results consistent with reduced functioning of appropriate areas of the cortex and as the symptoms resolve so do the electrophysiological abnormalities. This work is briefly mentioned in a later section.

#### 1.4.5 The headache

The headache phase may or may not be preceded by, or partially accompanied by, the above predominal symptoms. There may be dryness of the mouth, pallor or, occasionally, redness, excessive sweating despite a feeling of chilliness and cold, and there may be shivering or "tremors". The patient may smell of stale sweat in addition to having foul breath. In the more severe attacks the patient looks and acts prostrated, may be moaning, groaning or tearful, speaking slowly and without vigour, and if walking seems drooped or lacking in muscle tone. When the attack is mild enough to permit the patient to work they tend to give the impression of being tired and irritable. There is a temporary reduction in intellectual functioning during the headache and shortly afterwards (Willanger, 1975). Photophobia accompanies the headache in 70% of patients and this relates to the patient's desire to lie down in a darkened room (Pearce, 1976).

The pain is commonly limited to the head but may include the face, neck and shoulders. The headaches are usually unilateral in onset and tend to vary in their side of onset in successive attacks. Some people often have generalized headaches from their onset, and most unilateral headaches become generalised during the attack.

Migraine shares with other vascular headaches the features of depth diffusion, aching, and the rhythmic features of throbbing and pulsating. Generally the throbbing changes into a steady ache. Although there is some predictability concerning the site and duration of the headache in a given individual, the intensity and associated phenomena vary greatly. Intensity may vary from a barely perceptible ("background") headache to one of fierce intensity. The intensity is increased by

walking, bodily effort, a sudden change in position, bright light, loud sounds and mental effort. The headache is generally not sufficiently severe to prevent sleep, and sleep, although often fitful and broken, is regarded as the state of optimal comfort for the patient.

There may be localised tender spots which are often slightly boggy to touch. These places are hyperaesthetic and painful to pressure, and are associated with the presence of pain-sensitizing polypeptides of the kinin family. Spontaneous bruising may occur, although rarely, at some stage of an attack but it is unclear whether this is associated with the tender spots.

Anorexia accompanies most migraine headaches. It may be slight when the headache is of mild intensity, but severe headache is always associated with anorexia and usually with nausea. Pearce (1976) suggests nausea accompanies the headache in over 90% of patients. Vomiting, although common with severe headache, is usually absent, even with severe headache, if the duration is short. Vomiting sometimes immediately precedes the termination of the attack, although it may occur throughout the attack. The vomitus often is tasteless or bitter, becoming more acid towards the end of the attack. Dry retching is common in patients who have prolonged vomiting with their attacks.

Rubinowitz (1975) states that the associated symptoms of migraine headache such as nausea, vomiting and photophobia reflect only the intensity of the headache and are not specific for migraine, and also that they occur more frequently with migraine because these headaches are usually more severe than muscle contraction headaches. However, the gastro-intestinal symptoms are probably not a reaction to the pain



of migraine as they may occur with relatively mild headaches, and further they are probably not due to intra-cranial vasoconstriction affecting the medullary centres since they are not necessarily associated with vertigo and other symptoms of brainstem ischemia. Lance (1973) gives data suggesting changes in plasma serotonin may be linked with alterations of gastric motility. In some people the headache eases after vomiting. However in others vomiting may be the most serious aspect of the migraine attack, causing prostration during the attack, and delay in recovery after its termination. Patients with such severe vomiting are least likely to feel the usual buoyancy immediately following the termination of the attack. Due to the close association with nausea and vomiting migraine headaches are often referred to as "sick headaches" or "bilious headaches" by their victims.

#### 1.4.4 Frequency and duration of attacks

The attack may be of any duration, from a few minutes to several weeks. There may be short-duration, high intensity attacks; long duration, low intensity attacks, or any combination of the two. While attacks may begin at any time of day or night, the usual time of onset is in the early hours of the morning, and the commonest time of dissipation is in the early evening.

With regard to frequency, some patients have attacks predictably once or twice a week, others once a month, while others only three or four attacks in a lifetime. Furthermore, some patients have headache attacks once or twice a week for a period of four to six months, and then are free of attacks for three to five years. Still other patients may have frequent, even daily attacks for a week or so every three or four months, during twenty years or more, with freedom from attacks during the interim.

It is not yet clear what factors determine the frequency of attack although some of the underlying, precipitating and aggravating factors are known and these are considered subsequently (section 1.6).

#### 1.4.5 Usual after-effects of a migraine attack

Typically headaches are reported as lasting 12 to 36 hours and this usually means that normal activities can be resumed the day after an attack. Sometimes people feel tired, depleted or vaguely unwell for a day or two after the headache has subsided, especially if there has been a great deal of vomiting or diarrhoea. Other people feel relaxed, in good spirits, enthusiastic about their work, filled with energy and drive, and sometimes even overactive.

Other after-effects are uncommon apart from diuresis which may occur once the attack has passed its peak and is subsiding. This will be most noticeable in those who exhibited marked fluid-retention prior to the attack (see section 1.4.1).

After severe attacks or a cluster of attacks a refractory period may occur during which factors previously known to precipitate attacks are ineffective.

#### 1.4.6 Persisting or permanent sequelae

Migraine is regarded as a generally benign disorder, however a small minority of those experiencing migraine exhibit symptoms that persist for days or weeks after the headache subsides and, rarely, these may become permanent. Reports in the literature of death attributed directly to migraine amount to three cases in the past forty-five years (Guest and Woolf, 1964; Murphy, 1955). A study of these symptoms and their underlying mechanisms is of particular interest on two grounds. Firstly, such symptoms are reported as being accompanied by electroencephalographic (EEG) changes consistent with a reduction in function of the appropriate brain area, and may thus account for a proportion of the abnormalities found when EEG recordings are obtained between migraine attacks (see section 1.10). Secondly, when the symptoms become permanent it is assumed permanent brain damage has been caused, and it is conceivable that such damage might form an epileptogenic focus resulting in symptomatic epilepsy, a question considered more fully in section 1.9.

The persisting or permanent sequelae include visual field defects which may result from damage to the visual cortex, as in patients exhibiting homonymous hemianopia, or from damage to either retina. Pearce (1976) reviews some thirty-seven cases reported in the early literature, reports of cases suggestive of a lesion in the visual cortex include those of Connor (1962), Pearce and Foster (1965), Carroll (1968) and Boisen (1975), while ones reporting retinal lesions include Graveson (1949), Connor (1962), Carroll (1968), O'Connor (1975) and Gilbert, Rappaport and Trump (1974).

Perhaps the most often documented persisting symptom is partial paralysis following facioplegic migraine, ophthalmoplegic migraine or hemiplegic migraine. Such paralysis usually resolves over a number of days but may take several weeks and in some instances becomes permanent. Relatively few authors cite such cases caused by facioplegic or ophthalmoplegic migraine (Connor, 1962; Pearce and Foster, 1965; Boisen, 1975; and Pearce, 1975b), whereas a considerable number deal with the symptoms, and in some cases the EEG changes, associated with hemiplegic migraine (Clarke, 1910; Whitty, 1955; Connor, 1962; Bradshaw and Parsons, 1965; Pearce and Foster, 1965; Carroll, 1968; Bruyn, 1969; Verret and Steele, 1971; Beck and Manz, 1972; O'Connor, 1975; Dooling and Sweeney, 1974; Boisen, 1975; Gastaut, Giraud and Saint-Jean, 1975; Glista, Mellinger and Rooke, 1975; Pearce, 1975b; Johnson, 1976). Whitty (1955) suggested that there were two distinct forms of hemiplegic migraine and this distinction has been followed by many authors. On the one hand Whitty distinguished 'familial hemiplegic migraine' in which the weakness was always on the same side and lasted longer than the headache; consciousness was sometimes impaired; and there was a family history of hemiplegic migraine which involved the same side of the body and was of the same type as that of the patient. On the other hand, in the non-familial type, the hemiplegic episodes were experienced on one or other side of the body; they typically subsided slowly as the headache developed; the patient and his family often had ordinary attacks of migraine and some relatives were prone to hemiplegic episodes. Clearly, familial hemiplegic migraine typically shows a persisting defect but both types may, on occasions, result in a permanent defect.

Other persisting or permanent sequelae include sensory loss (Connor, 1962; Boisen, 1975), ataxia (Golden and French, 1975) and psychic disturbance. The latter commonly takes the form of a feeling of unreality, mild confusion and poor judgement lasting hours or days (Carroll, 1968; Hachinski, Porchawaka and Steele, 1973) although on rare occasions there may be lasting impairment (Murphy, 1955) or dementia (Connor, 1962; Carroll, 1968; O'Connor, 1973; Boisen, 1975 and Klee, 1975b) and other types of psychiatric illness have been implicated (Bruyn, 1969).

When considering the underlying causes of these persisting or permanent sequelae of migraine authors note that the classical concept of migraine suggests an initial phase of vasoconstriction of cerebral vessels, causing the aura, to be followed by vasodilation of scalp vessels, causing the pulsatile headache. Recent studies have confirmed that cerebral blood flow is reduced during the aura (Simard and Paulsen, 1973; Simard et al, 1973; Skinhøj, 1973; Norris et al, 1975; Mathew, Hrastnik and Meyer, 1976) but in some parts of the brain the flow reduction may be sufficiently severe to reach critical levels of oxygen supply and the reflex increase in flow normally caused by inhaled carbon dioxide is extinguished. Skinhøj (1973) and a leading article in the British Medical Journal (1977) report that lactic acidosis has been found in the cerebrospinal fluid of selected patients with focal neurological symptoms in the prodromal phase, which is a potentially serious condition associated with cerebral vasomotor paralysis and paradoxical responses of blood flow to both constrictor and dilator drugs.

Given these conditions it is not surprising that occasionally migraine can cause prolonged ischemia which may proceed to edema and possibly to infarction. It is not yet known what factors cause the localization of the major zones of ischemia when there is a general reduction of blood flow, nor what prolongs the ischemia to an extent sufficient to produce death of brain tissue.

The presence of ischemia, edema and infarction and their anatomical extent can be demonstrated, as can their resultant physiological effects, by objective measurement. The electrophysiological changes associated with various migraine aura and with the persisting or permanent sequelae can be shown using electroencephalographic or evoked potential techniques (see section 1.10). Evidence also comes from measurements of cerebral blood flow (see above), radionuclide brain scanning (scintigraphy), angiography, and the recent introduction of computer assisted axial tomography (CAT). In addition there has been direct observation of retinal changes (Bickerstaff, 1967; Piovela, 1972; and Gilbert et al, 1974) but these are not always seen (Joffe, 1973).

Angiography has been used by a number of authors (Whitty, 1953; Murphy, 1955; Connor, 1962; Bradshaw and Parsons, 1965; Pearce and Foster, 1965; Carroll, 1968; Bruyn, 1969; Skinhøj, 1973; Norris et al, 1975 and Pearce, 1975b). Findings include abnormal filling of blood vessels, narrowing of vessels and occlusion of vessels, but some normal responses are seen. The reports of normal findings are difficult to interpret since often the time of recording in relation to the attack is not given, and one would expect a return to normal after the attack in most cases. However, while angiography

is occasionally needed to exclude a tumour, angioma or aneurysm, it is recommended (Rubinowitz, 1973; Pearce, 1975b; Leading article BMJ, 1977) that this be delayed until several days after the attack, when the vasomotor and neurological status has stabilized again. This is because migrainous subjects seem to be at increased risk from angiography, having attacks exacerbated or a thrombosis precipitated.

The use of CAT scans (Cala and Mastaglia, 1976a, 1976b; Hungerford et al, 1976; Mathew, Meyer and Welch, 1976; Mathew et al, 1977) has the advantage of being a non-invasive technique and in many patients shows, between attacks, no abnormality despite lifelong severe migraine. Abnormalities usually shown include cerebral parenchymal low densitometric areas suggestive of infarction, ventricular enlargements and cortical atrophy. The cerebral parenchymal low density areas tended to disappear on repeat scanning and it is suggested these are the result of edema. Focal atrophy, a recognised sequel of infarction, correlates in some cases with the patient's symptoms.

It should be re-emphasised that only a small minority of the migrainous are thought to suffer persisting or permanent sequelae, but no figures are available. Such cases of hemiplegic migraine as are reported in the literature rarely mention that children may be affected, so that when three such children were seen at the Neuropsychology Unit it was felt worthwhile to report these in a paper (Harding, Debney and Maheshwari, 1977). As this report did not arise as a direct consequence of the research programme, its details will not be considered here.

### 1.5 The size of the problem in the population

If the incidence of migraine is as reported, then one can estimate that the financial loss to industry is already substantial. Additionally, if it is true that women are more susceptible than men then this matter of the cost to industry becomes even greater as more women necessarily enter industry. Looking at society in general the misery which must arise from migraine is undoubtedly substantial. One wonders how much the accident rate in industry and at home is caused by interference to normal vision alone, quite apart from other characteristics. These wider aspects of industry are dealt with by the Office of Health Economics (1972) and cannot reasonably be dealt with in this section which is seeking to establish more firmly the methodology of this investigation.

Thus the purpose of this section is:-

1. to estimate from the literature the true incidence of migraine in the population for males and females, bearing in mind
  - (a) the non validity of some criteria used hitherto,
  - (b) the reported overlap between migraine and epilepsy
 (see section 1.9).
2. there is a popular assumption that migraine is related to higher intelligence and higher social-class. Since it was intended to examine a number of university students, who are assumed to be intelligent and who are likely to contain a disproportionate number from the "middle-class", it was important to verify whether these factors would unduly affect the student population and thus the sampling.
3. Some authors had used the presence of certain other conditions as supportive evidence for a diagnosis of migraine and it was wished



to verify how useful these would be to include in Headache Questionnaire 2 as a check on potential volunteer control subjects if their freedom from migraine was at all suspect (see section 2.1 and 2.2).

Using the information obtained to meet the first two aims it was hoped to ensure that a large enough student population could be selected which would contain a sufficient sample of truly migrainous students, and at the same time to keep that population small enough to be adequately used in the time with the facilities known to be available. It was realised quite soon that the numbers involved could lead to a critically difficult experimental situation.

#### 1.5.1 Incidence in the population and the drawbacks of most estimates

Estimates of the incidence of migraine in the population have ranged widely. At the extremes Lance (1973) states "one author alleged that 60% of the population suffered from migraine" whereas Waters (1975e) cites another study giving the prevalence of migraine as 0.5 per cent. Generally authors will take a figure of 5 to 10 per cent as an acceptable estimate (Hanington, 1973; Rubinowitz, 1973; Sargent et al, 1973; Parkes, 1975). However, as Waters (1975e) points out "the mean of a series of incorrect estimates does not necessarily give a true figure". The variation in estimates is attributable to differences in diagnostic criteria, methods of data collection, materials and analysis of results.

#### 1. Diagnostic Criteria

Problems of defining and, thus of diagnosing, migraine, were discussed previously. Where studies cite definitions, these vary considerably. Indeed at least one important longitudinal population study, the Isle of Wight study (Rutter et al, 1970) excluded migraine because of difficulties in definition.

## 2. Methods of Data Collection (1) - Interviews and questionnaires

Because of the lack of objective parameters, diagnosis, whatever the definition, is based on information provided by the individual in response to written or spoken questions, the construction, objectivity and delivery of which may markedly affect the answers. This is important when considering interview and questionnaire methods.

Dalsgaard-Nielsen, Engberg-Pedersen and Holm (1970) advocate interviews as providing a full picture of the symptoms and clinical history of each individual and regard the sole use of a questionnaire as somewhat rigid, producing an incomplete picture. Yet it is because each subject is treated the same that any differences found in a questionnaire study are more likely to reflect differences in the people studied and not reflect differences in technique (Waters, 1975c). In this study both techniques were used (see sections 2.1 and 2.2).

## 3. Methods of Data Collection (2) - Records

Some studies have used medical records to estimate migraine prevalence. In Britain the apparent advantage of medical records is that under the National Health Service, all children and adults are eligible to be on the list of a general practitioner for medical care. While nearly everyone takes the opportunity, the use of medical records has two major drawbacks. Doctors vary in the amount and quality of the information they record and often this is inadequate for research (Rutter et al, 1970). Secondly, as will be shown later, not all migraine sufferers consult their doctor for this complaint. Figures such as those of Walker (1959) who estimated a prevalence rate of 4.85 per cent, are therefore underestimates.

#### 4. Population Samples

A large part of the variation in estimates of population incidence of migraine can be directly attributed to variation in sampling. Samples selected for study have included patients admitted to neurological or other special hospital departments; patients undergoing treatment for migraine as out-patients or attending specialists; patients in a general practice; particular occupational groups; and persons of specified age groups in a defined geographical area. These and their drawbacks are discussed below.

4a. Waters (1975e) points out that "in order to give a prevalence one must know the population from which these cases were derived" a point also made by Hay (1975). Often this is unknown, but even if it is known, for example, the register of a British general practitioner, it is unjustified to assume that all patients with migraine come for treatment. Bille (1975a) found only one-third of a group of school-children with severe migraine had attended a doctor on account of their headaches. Similarly Fogelman (1976) reported that 11% of over eleven thousand sixteen year olds reported migraine or recurrent sick headaches in the previous twelve months, but only one-third of these had consulted a doctor in this time about them. Waters and O'Connor (1970) calculated that 19 per cent of women aged between 20 and 64 years of age living in the Rhondda Fach had had at least one attack of migraine in the year preceding the survey. Yet in their validation group, only 23 per cent had consulted any doctor in the previous 12 months because of their headaches and only 54 per cent had ever seen a doctor about them.

4b. In the absence of figures for the population from which patients are drawn, the cases of migraine may be given as a proportion of all patients attending that doctor or clinic (e.g. Selby and Lance, 1960) this may give a distorted indication of migraine prevalence not only because different conditions may have different consultation rates, but also because doctors known to be specially interested in a particular condition may attract such cases.

4c. In studies based on patients attending doctors these patients are not necessarily representative of all sufferers. Similarly, if there is a low rate of co-operation in studies of a defined population, such as an occupational group or geographical area, (e.g. Childs and Sweetnam, 1961, had a questionnaire return rate of only 54 per cent) those who do not co-operate are not necessarily similar to those who do. There is evidence to suggest dissimilarities exist. For example, Waters (1972a) found those replying to the initial postal questionnaire were more likely to have headache and migraine. Equally there is evidence suggesting that migraine sufferers of higher social class or higher intelligence are more likely to consult their doctor (Waters, 1971c).

## 5. Analysis of Results

Finally, many studies give a single figure for population prevalence. This is misleading on two counts. Firstly, most studies show migraine to be more common in women, Refsum (1969) reviews the literature in this area. Secondly, migraine attacks occur less frequently in childhood and old age (see below).

### 1.5.2 Incidence in the population - likely estimates

Given the above considerations, very few authors provide suitable information. Noteworthy is the pioneering work on children by Bille (1962, 1969, 1975a, 1975b) on 8,995 school children aged 7 to 15, in Uppsala, Sweden; the subsequent studies of Dalsgaard-Nielsen (1970), his co-workers (Dalsgaard-Nielsen et al, 1970), and the study by Sillanpaa (1976). When considering adults the estimates made by Dalsgaard-Nielsen et al (1970) will be compared with the figures found by Waters and his co-workers in a series of studies in different areas and occupations in Britain (Waters, 1970a; Waters and O'Connor, 1970; Waters and Cochrane, 1970; Waters, 1971a, 1971c; Waters and O'Connor, 1971; Waters, 1972a, 1972b, 1973a, 1973b, 1974a, 1974b, 1975a, 1975b, 1975d, 1975e; Waters and O'Connor, 1975). Waters (1975e) summarizes the results of these studies.

The incidence of migraine in the population is seen to vary with age. It is difficult to diagnose the syndrome in young children both because of the patient's inability to provide detailed information and because migraine variants are frequently found in this age group. However migraine has been diagnosed in children in the first three years of life (Trued, 1974; Golden and French, 1975; Prensky, 1976; Sillanpaa, 1976; Bille et al, 1977). It probably occurs infrequently before the age of seven, at which age Sillanpaa (1976) estimates the prevalence to be 3.2%, whereas Bille and his co-workers (1962, 1969, 1975a, 1975b, 1977) found the incidence at 7 years to be 1.4 per cent, from which point it rose slowly to 5.3 per cent at 15 years. In these children the incidence was similar in boys and girls up to the age of eleven, thereafter girls were more often affected and the difference increases with age. At the age of 15 the boys showed a migraine

prevalence of 4.0 per cent and the girls of 6.4 per cent. The estimates given by Dalsgaard-Nielson et al (1970) are somewhat higher at all ages than those of Bille being at 2.9 per cent (as compared with 2.5 per cent) for the 7 to 9 age group and again shows a bifurcation of rates, as between boys and girls in their teens. They found the onset of migraine in adolescent females is often correlated with menarche. The prevalence rate increased relatively rapidly during the teens and early twenties, then slowed, with little increase after the age of 30 in men and 40 in women. They found the incidence in women had reached 18.8 per cent by the age of 40 and the corresponding figure for men being 11.2 per cent. The figure for manifest migraine, that is all those who have ever had migraine, in women given by Dalsgaard-Nielson et al (1970) would superficially appear to be in good agreement with the oft-quoted figure from Waters and O'Connor (1970, 1971) of a prevalence of 19 per cent in women aged 20 to 64 years. However, both these estimates are likely to under-represent the figure for total manifest migraine. That of Dalsgaard-Nielson et al., because they based their figures on a patient sample, while that of Waters and O'Connor is for those who had had a migrainous episode in the last year, and thus those who had attacks previously but have since had remission of their attacks, are not represented. Indeed subsequent surveys in various populations have shown that the prevalence of migraine is 15 to 20 per cent in men and 24 to 29 per cent in women (Waters, 1974a; Waters and O'Connor, 1975).

The final figures quoted above indicate a female:male ratio of 1.5:1 and Bille (1962) in his unselected material found the same ratio in his oldest group, that is 13 to 15 years. Refsum (1969) reviews the literature, and the figures given from clinical practice vary from a

female:male ratio of 4:1 to 1.3:1. Refsum suggests that this difference in sex distribution of clinical material could be explained by the suggestions that women may be more seriously affected by their migraine than men and also that women may have a greater tendency to seek medical advice. He reviews the genetic aspects of migraine and concludes there is no evidence to indicate sex-linkage of migraine, even if some degree of sex-influence appears to be present. It should also be remembered in relation to this question of female:male ratio that the menstrual cycle is regarded both as an aggravating factor and a provoking factor in migraine in women.

#### 1.5.5 Relationship of migraine to intelligence, social class and various disorders and diseases

Early papers on migraine suggested a positive correlation with both intelligence and social class and is a view often held popularly (Walsh, 1957; Childs and Sweetnam, 1961; Barolin et al, 1974). This popular view may have been influenced by the number of famous people known to suffer migraine (Critchley, 1967; Sacks, 1973; Friedman, 1975b), including Charles Darwin, Karl Marx, Sigmund Freud and Lewis Carroll. However, when these assumptions were investigated (Childs and Sweetnam, 1961; Waters, 1971c; Arthur, 1974; Barolin et al, 1974; Rees, 1974), the weight of the evidence suggests that no such correlations exist, but that those of higher intelligence or social class are more likely to consult their doctor. Perhaps this is because, as Childs and Sweetnam found, those who had to think and make decisions as part of their work were more often unable to continue than were those doing manual work.

Migraine has also been suggested to occur in relation to such conditions as a past history of vomiting in childhood; epilepsy; allergy and hypertension. As discussed earlier, vomiting attacks in childhood are now accepted as a migraine variant in children, which often converts to more typical attacks later in life. An association with a personal history of motion sickness is supported by several authors (Selby and Lance, 1960; Bille, 1962 and Refsum, 1969). Refsum found that his migraine groups showed a tendency towards a higher incidence of travel sickness, abdominal pain and vomiting in childhood than the non-migrainous but the differences did not reach statistical significance.

The evidence concerning any relation between migraine and epilepsy is discussed separately later (section 1.9).

With regard to allergy, Maxwell (1966) gives a good review of the arguments for and against an association of migraine with allergy, coming to the conclusion that there is little supporting evidence for it. This observation makes it clear that evidence for a primary relationship with allergy is lacking, but it does not deny the possibility of migraine being triggered off by allergic disturbances. This view is shared by others including Hay (1968, 1971, 1973); Sacks (1970); and Lance (1973) with the allergic disorders implicated including asthma, allergic rhinitis including hay-fever, eczema or urticaria, and rheumatic fever (now accepted as being a form of allergic reaction to streptococcus).



With regard to hypertension, it is known that this condition can cause headaches (Delassio, 1972) but a relationship, if any, between migraine and hypertension has yet to be clarified. Waters (1971b), in a community based study, found the number of individuals that could be regarded as hypertensive was small. He concluded from this study that most individuals with headache, and with migraine, have blood pressures similar to those who do not have headaches. Leviton et al (1974) criticized Waters' work on the grounds that to evaluate the relationship of migraine to hypertension two requirements must be met. Firstly, that the population studied be not selected by virtue of medical care, and this Waters' study did do. Secondly, that a relatively large number of people at risk of both migraine and hypertension be studied, and that since hypertension increases with age, the population studied should be composed mainly of middle-aged and elderly people. This latter requirement was not met by Waters since his migraine population over the age of 55 years was composed of 7 men and 13 women. In their own study, which they claimed met their two requirements, Leviton et al concluded that there was an association between migraine and high blood pressure. However, they selected as their sample the parents of migraine patients, and it cannot necessarily be assumed that these constitute a representative community sample. Even so, the possibility of a relationship between migraine and hypertension remains.

To summarize, there is no demonstrable relationship between social class or intelligence and migraine; the question of a relationship between migraine and epilepsy is considered later; the role played by allergy in migraine is more suggestive of a trigger factor than of a primary relationship; the possible relationship between migraine and hypertension needs clarification and finally there is good evidence of

an association between migraine and both a history of childhood vomiting attacks and a history of travel-sickness.

### 1.6 Precipitant (trigger) factors

One of the features of interest in this investigation of migraine is that migraine sufferers report a variety of triggers for their attacks including visual stimuli. Of the several questions that arise in this area those of particular interest include:-

- (a) What are the trigger factors?
- (b) What percentage of migrainous people are affected by them?
- (c) What are the possible explanations of how they trigger migraine?

When considering the explanations of how they trigger migraine these will be recorded and compared in search of a basic pattern. It is recognized that a study of the preventative therapies, where successful, might aid the understanding of the trigger mechanisms, yet this aspect has been for the main part omitted though a few examples are quoted, where they seem relevant to this study, at this stage.

Arising out of the analysis of the literature in this area it was hoped to develop two further tools.

- (a) a check-list of trigger factors, also to be included in HQ2 (see section 2.1.2).
- (b) to prepare a questionnaire based on visual precipitants of migraine to be used in structured interviews (see section 2.1.3).

It should be noted additionally that the check-list mentioned in (a) above might well enable a researcher to check whether there is a discontinuity between normal subjects and migrainous subjects when subjected to trigger stimuli or whether the population lies on a continuum.

It should also be noted with regard to question (b) that if a suitable questionnaire is developed it could be used to compare the visual stimuli triggering migraine with those triggering photosensitive epilepsy.

#### 1.6.1 An overall view of precipitant (trigger) factors

On examining the literature an enormous list of trigger factors emerges and Table 1.1 reproduces the list of factors compiled in 1971 by the Migraine Trust and quoted by Office of Health Economics (1972); Hanington (1973) and the Migraine Trust (1975). In order to make a rational consideration of the factors, Graham (1969) makes a division into those of the internal and those of the external environment.

"The normal subject's cranial blood vessels respond to stimuli from within or without the body by vaso-constriction and secondary vasodilation in a physiologic fashion without the production of symptoms." (see Fig. 1.1.a). "The migraine subject, on the other hand, responds excessively, or aberrantly to these same stimuli with resultant impairment of function from ischemia and a reaction productive of abnormal tissue physiology and even damage, requiring repair". (see Fig. 1.1.b).

Graham then proceeds to list "common stimuli and events that produce migraine" under the three headings of external environment, physiologic environment and psychologic environment, and these are reproduced in Table 1.2. A cursory glance comparing the two lists quoted in Tables 1.1 and 1.2 will show that there are many common features. However, Graham's division of the factors into three groups is somewhat artificial as all of them can be presumed to act by influencing the internal state of the individual, and his diagrams reproduced in Fig. 1.1 might be improved by showing the arrow from the 'external environment' having to pass through the 'internal environment' in order to cause vasoconstriction.

TABLE 1.1 A list of triggering factors quoted by Office of Health Economics (1972), Hanington (1975) and the Migraine Trust (1975), who reproduced it from 'Focus on Migraine' published in 1971 by the Migraine Trust.

Anxiety	Prolonged focusing on T.V. or cinema screen
Worry	
Emotion	Very hot baths
Depression	Noise, particularly loud and high pitched sounds
Shock	Intense odours or penetrating smells
Excitement	
Over exertion	Certain foods, for example: fried foods chocolate citrus fruits pastry cheese
Physical and mental fatigue	
Bending or stooping, as in gardening	
Lifting heavy weights or straining of any sort	Use of sleeping tablets Alcohol
Change of routine, e.g. holidays, shift-work, or change of job	Prolonged lack of food, fasting or dieting Irregular meals
Late rising especially at weekends or on holiday	Menstruation and the pre- menstrual period
Travel	Menopause
Change of climate	High blood pressure
Changes in weather	Continued use of oral contraceptives
High winds	
Bright sunlight, bright artificial light or glare of any kind: fluorescent light	Toothache and other local pains in head or neck

TABLE 1.2      The list of 'common stimuli and events that produce migraine' reproduced from Graham (1969).

External environment

- (a) bright light, noise, smells
- (b) barometric changes
- (c) anoxia from any cause
- (d) temperature changes
- (e) certain medicines and foods such as nitrites, histamine, dexedrine, reserpine, alcohol, nicotine, chocolate, cheese and other tyramine-containing foods

Physiologic environment

- (a) hypoglycemia
- (b) insomnia
- (c) menstrual cycles
- (d) syncope
- (e) accesses of hypertension
- (f) fever
- (g) excessive exercise
- (h) dehydration
- (i) allergic reactions

Psychologic environment

- (a) prolonged mental strain
- (b) prolonged and excessive alertness
- (c) anxiety
- (d) anger
- (e) depression

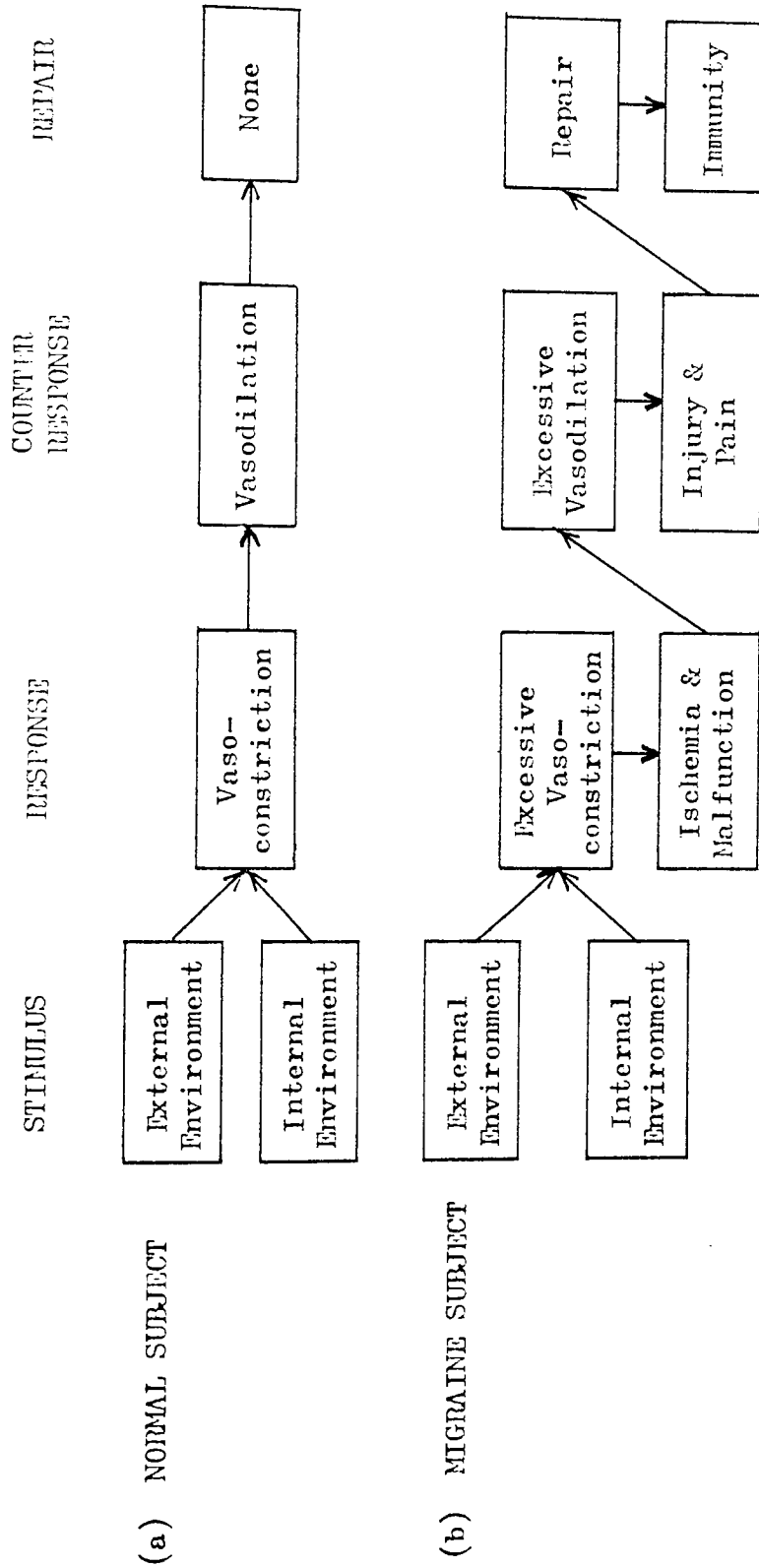


FIG. 1.1.1 Flow diagrams reproduced from Graham (1969) illustrating the course of events following stimulation by a factor or factors that may produce migrainous headache.

Other authors mentioning precipitant factors of migraine also tend simply to list them and relatively few have attempted to ascertain the numbers or percentage of their patients, or of the migraine population generally, affected by particular stimuli. Considering first those authors simply citing precipitants, Table 1.5 was prepared in order to gain an overall impression of the weight of opinion supporting suggested factors. In order to prepare this table the list of precipitants was simplified by combining some closely related factors and by omitting others. The factors omitted were those appearing in only one list as follows:- syncope (Graham, 1969); dehydration (Graham, 1969); smoking (Duke-Elder, 1949); change of routine (Table 1.1) and 'bending or stooping in gardening' (Table 1.1). This last factor could be a matter of physical fatigue but might include a postural phenomenon and was therefore not combined with that of 'fatigue or excessive exercise'.

Turning to the categories containing a combination of related factors, two require some explanation. Firstly, 'emotional or mental stress' is intended to include both marked pleasant and unpleasant emotions such as excitement, shock, anxiety or anger as well as prolonged mental strain or alertness. Secondly, 'illness' includes stimuli termed 'fever' or 'acute infection'.

Table 1.5 reveals what factors various authors feel may be relevant in precipitating attacks of migraine and could be assumed to be influenced by

- (a) the numbers of their own patients (if they are practising doctors) who report the various trigger factors.



**TABLE 1.3** Precipitant (Trigger) factors of migraine cited by various authors

Trigger Factors	Duke-Elder (1949)	Malsh (1957)	Catino (1965)	Graham (1969)	Blau (1970)	Hanington (1973)	Lance (1973)	Rubinowitz (1975)	Sacks (1973)	Rees (1974)	Friedman (1975b)	Raffaelli & Menon (1975)	Speer (1975)	Wakefield (1975)	Nightingale (1976)
Psychological Factors															
Emotional/ Mental Stress	x	x		x	x	x	x		x	x	x	x	x	x	x
Relaxation/ After Stress	x			x	x	x			x	x					
Migraine Personality			x					x							
Depression				x		x									
Fatigue/excessive exercise	x	x		x		x	x		x		x	x		x	x
Insomnia				x	x				x	x					
Sleeping late					x	x			x	x					
Lack of food	x			x		x	x	x	x	x	x		x	x	x
Allergic reactions				x									x		x
Hormonal (female)				x	x	x	x	x	x		x	x		x	x
Illness				x			x		x				x		
High blood pressure				x		x	x								
Head/neck pains						x			x						
Certain foods	x			x		x	x			x	x		x		
Alcohol	x				x	x	x	x	x	x			x		x
Certain drugs				x		x	x	x			x		x		
Weather changes	x			x		x			x		x	x	x		
Changes/extremes of temperature				x	x	x		x	x				x		
Motion/Travel						x			x			x	x		
Smoking	x														
Fumes & odours		x		x		x	x		x		x	x			
Noise				x		x	x		x		x	x			
Visual factors	x	x		x		x	x	x	x		x	x	x	x	x

- (b) the authors' particular interests. Some authors seem especially influenced by their own interests, e.g. Catino (1965) and Rees (1974) in psychiatry and Speer (1975) in allergy.
- (c) the wealth of publications on any one factor, with certain ones receiving particular attention by researchers in recent years, e.g. the role of female hormones and the influence of dietary factors.

Thus while those authors included in Table 1.3 help indicate the range of possible factors and the weight of opinion supporting them, they do not necessarily indicate the relative importance of the factors in the migraine.

It was hoped a study of the various papers indicating what percentage of the migrainous were affected by particular factors would help reveal which of these affected most people and how relatively important visual stimuli are. Six authors were found to have given such figures, which are given in Table 1.4, and as they were obtained from a variety of sources these are given below:

- (a) Selby and Lance (1960) working in Australia examined 300 women and 200 men attending a neurological centre.
- (b) Bille (1962) obtained his figures from a group of 32 boys and 41 girls, aged 9 to 15 years, with pronounced migraine. These were selected from 8,993 schoolchildren in Upsala, Sweden who participated in Bille's main survey.
- (c) Pearce (1971, 1976) obtained his figures from 450 patients attending a Headache Clinic in Hull, England.

- (d) Hay (1973) working in England studied 67 men and 177 women attending any one of four doctors who co-operated with the survey.
- (e) the figures quoted from Henryk-Gutt and Rees (1973) are from retrospective data obtained from English Civil Servants consisting of 50 men and 50 women with half of each having classic migraine and half common migraine.
- (f) Arthur (1974) obtained his figures from 55 men and 67 women patients in New Zealand.

Unfortunately, it is difficult to judge the relative importance of the various factors on two grounds. On the one hand, although precipitants are often reported, it does not necessarily follow that absence of a precipitant in a report indicates that it was not a precipitant, rather that it was not reported as such. On the other hand the methods used to obtain the information vary. Bille (1962) obtained his figures by asking the children to mention up to five of the commonest factors which usually provoked their migraine attacks. Hay (1973) states that patients were asked to consider separately each of a number of precipitating factors and to indicate whether they thought each factor was associated with the onset of an attack. Unfortunately it is not clear whether the factors Hay then discusses comprised the total list or not. The other authors do not give details of their method of enquiry apart from Henryk-Gutt and Rees (1973) who gave some details of their semi-structured interview technique.

Despite the variation in the samples and the research methods, a number of points arise from the figures in Table 1.4 and these are summarized below.

1. All authors found emotional or mental stress to affect at least one-third of all their patients with total estimates ranging from 37 to 73 per cent.
2. Relaxation after stress also affects a significant, although smaller, proportion with estimates ranging from 17 to 45 per cent. Bille does not quote a figure for this category but in a later paper (Bille, Ludvigsson and Sanner, 1977) states that in children "the attacks develop, as in adults, after the stressful situation."
3. The category of physical exertion is a little difficult to interpret as Bille and Arthur subdivide this group and Pearce combines it with sleeplessness, but it is apparent this factor affects a fair number of people, although less than emotional or mental stress.
4. In adult women the hormonal changes associated with the onset of menstruation can precipitate migraine in between 34 to 62 per cent of women. Bille's figure comes from those 20 girls who had started menstruating and are difficult to interpret both because that is a small group and because the age of onset of migraine in females has been shown to be influenced by the age at which menstruation starts (see section 1.5).
5. All the authors cite food substances with the majority indicating that 20 to 26 percent of adults are affected. Alcoholic drinks do not feature as a precipitant in the list given by Selby and Lance since they excluded alcohol drinks

TABLE 1.4

The occurrence (per cent) of trigger factors found by the listed authors in their patients or the migrainous group they studied. All were adult groups except for the group of migrainous school children studied by Bille.

(M - males affected as percentage of males;

F - females affected as percentage of females;

T - percentage of total population affected).

	Selby & Lance (1960)	Bille (1962)	Pearce (1971, 1976)	May (1973) (67 men and 177 women)			Henryk-Gutt and Bees (1973) (50 men and 63 women)			Arthur (1974) (35 men and 67 women)		
	T	T	T	M	F	T	M	F	T	M	F	T
Emotional/Mental Stress	67	59	73	27	45	40				20	46	37
School stress (exams)		33										
Concentration												4
Anger, frustration							40	54	47			
Work problems							66	50	58			
Personal problems							64	60	62			
Relief of strain, weekends			45				26	46	36	11	19	17
Physical exertion		25								9	9	9
Fatigue		11	43*			15						
Bending, lifting										20	10	14
Gardening												3
Loss of sleep/ oversleeping							40	20	30			1
Lack of food		25	7				36	30	33			4
Allergic reactions	**	**				**						
Hormonal (female)		***										
	62	12	39		44						34	
Common cold		8										
Minor head injuries										11	3	6

\* includes "fatigue/sleeplessness";

\*\* while not finding allergic reactions to function as a trigger, these authors found an apparently high history of allergy and this may be of relevance (see text);

\*\*\* "out of 20 girls"; not all girls having started menstruating.

TABLE 1.4 cont'd.

	Selby & Lance (1960)	Bille (1962)	Pearce (1971, 1976)	Hay (1973) (67 men and 177 women)			Henryk-Gutt and Rees (1973) (50 men and 65 women)			Arthur (1974) (35 men and 67 women)		
	T	T	T	M	F	T	M	F	T	M	F	T
Certain foods	26	5	15			25	16	24	20	23	25	25
Fatty foods						14						
Alcoholic drinks			10				22	10	16	43	30	34
Sleeping tablets												1
Weather changes		3										
springtime												1
wind		5										1
Heat		7										4
Cold		5										5
Travel		15								11	28	23
Smoking												3
Fumes & odours		3										4
Noise		19								6	7	7
Visual factors	47					24*						
Sunlight										20	36	30
Glare, shimmering light			30							9	18	15
Eye-strain, films, TV.												5
Stroboscopic effects		** 84										
Darkness												1
Environment, weather, lightning, etc.							28	14	21			
No triggers known										11	12	12

\* "excessive sensory stimuli, usually glare and flicker"

\*\* included 36% sitting "too near in cinema or in front of television", 14% affected by "sun-reflections from sea or snow" and 34% affected by "both cinema or TV and sun reflections".

"as vasodilation is the probable mechanism of headache following alcohol, rather than idiosyncrasy to a food."

Subsequent research was to suggest that certain constituents, such as tyramine, might be the cause instead (Curzon and Hilton, 1975) and these are considered with other dietary factors later in this chapter.

6. Visual stimuli emerge as one of the major factors reported with between a quarter to one-half of the adults affected. However, 84 percent of the children Bille studied quoted a visual precipitant. It is not clear whether this higher incidence reflects the composition of the group (they all had pronounced migraine), relates to the amount of cinema and television watched (if children watch more), reflects an age factor in visual sensitivity or a combination of these.
7. The sex differences in susceptibility to different triggering factors, as reported do not show any overall consistent trend.

The relevance of these points and the data in Table 1.4 to this study is as follows:

- (a) they serve to confirm the majority of the wide range of trigger factors listed in Tables 1.1 and 1.3 which is of use when compiling the check-list of trigger factors for Headach Questionnaire 2 (see section 2.1).
- (b) they indicate the relative importance of visual stimuli as ranking perhaps slightly higher than dietary factors and as being probably the third most important factor after emotional or mental stress and menstrual hormones.

- (c) the relative importance of psychological factors, diet and the menstrual cycle hormones suggest that ideally they should be controlled for or taken into account in any study of visual stimuli.

#### 1.6.2 Underlying mechanisms - some difficulties

Some factors are not considered further because there is no adequate explanation of their influence, these include sleeping tablets, minor head injuries, illness, smoking and noise. Smoking was investigated by Volans and Castledean (1976) who concluded it is unlikely to be a factor in the aetiology or the exacerbation of migraine. Noise does not appear to have been investigated, although as Hay (1975) refers to excessive sensory stimulation, and Sacks (1973) to arousal migraine, perhaps the effects of noise can be understood in terms of the stress reactions considered in section 1.6.3.

Two other factors, insomnia and over-sleeping are considered symptoms of the onset of the condition rather than the causal agents. In the normal individual insomnia is a symptom of over-arousal, such as that caused by emotional stress or physical fatigue, and over-sleeping commonly occurs after the over-arousal, (Cameron, 1974; Nightingale, 1976).

As emotional stress, physical fatigue and relaxation after stress are all known precipitants of migraine it is not surprising if the migraine is associated with sleep disorders. Herberg (1975) suggests both insomnia and oversleeping may be effects of changed levels of serotonin (also known as 5-hydroxy-tryptamine or 5-HT) and noradrenaline affecting hypothalamic function and such biochemical changes are seen during



migraine attacks. As such biochemical changes are known to follow consumption of certain foods, (discussed later in this chapter) these have also been incriminated as causing both the sleep disorder and the migraine (Rubinowitz, 1973; Arthur, 1974). However, both Rubinowitz (1975) and Pearce (1976) highlight the situation where oversleeping or late-rising may indirectly cause migraine as a result of lack of food.

Finally some proposed factors are regarded as misleading in the sense that they may feature as aggravating factors, i.e. they may increase either susceptibility to attacks or the severity of attacks, rather than act as trigger factors. Both hypertension and allergy fall into this category as is shown below.

The early work of Walker (1959) suggested migraine patients are unduly subject to essential hypertension. However, Waters (1975e) examines the literature, including his own study (Waters, 1971b) and concludes that blood pressure is not an important factor in the prevalence of migraine in the community, although it is possible that there is a small group of hypertensives in whom headache is directly related to their high blood pressure. The view that hypertension aggravates or accentuates migraine is generally accepted (Graham, 1969; Lance, 1973; Waters, 1975e; Pearce, 1976), and it is possible the early work of Walker (1959), working in general practice, was distorted because the migrainous individual with hypertension is more likely to go to the doctor to obtain relief.

When considering allergy, some authors refer to adverse reactions to certain foods as food allergy (Speer, 1975; Nightingale, 1976), but this is misleading for as Pinna and Vanselow (1976) point out foods may contain substances which provoke headaches on a non-immunologic basis, and such dietary factors are thus considered separately later. Even so, migraine and allergic reactions have certain common features, particularly changes in size and permeability of involved blood vessels, and if the two conditions occur concurrently one could expect an increase in the distress experienced by the sufferer. Moreover histamine may act as a pain-sensitizer (see section 1.9). On these grounds it is not surprising that Selby and Lance (1960) found histamine therapy (essentially a desensitization course of treatment) to be beneficial in many patients, whether or not they had a personal or family history of allergic disorder. Waters (1972c) and Hay (1975) suggest a relatively high proportion of migraine patients report a history of allergic disorder but both conditions are frequently found in the general population and Pinna and Vanselow (1976) conclude that the statistical evidence supports the view that migraine is only rarely caused by allergy. Apart from allergic reactions exacerbating an attack, individuals suffering allergic disorders such as hay-fever or asthma may be less able to cope with their life situation and thus under some emotional or mental stress. Any such stress already present would make them closer to the threshold for a stress provoked migraine, and thus more susceptible to other stresses. The mechanisms for stress provoked migraine are discussed later.

Speer (1975), a specialist on allergy, wonders if the fumes and odours which may precipitate migraine should be classified as allergens. He lists a wide range of such fumes and odours including perfumes and

colognes, smoke, paint thinner, diesel exhaust, hair spray, newsprint, tar and asphalt, cooking odours, soap powder, floor wax, furniture polish, chlorine, ammonia, stencils, wash-and-wear fabrics and various industrial chemicals. No work appears to have been done on such fumes and odours in relation to migraine with regard to their biochemical constituents and the allergic, vasoactive or biochemical reactions these produce in the body.

#### 1.6.5 The search for common underlying mechanisms - (1) Psychological aspects

As psychological aspects are likely to influence the experimental subjects of this study, these aspects are considered in some detail.

Merskey (1975) reviews the early literature linking personality and migraine. Wolff (1965) described a typical migraine personality as being stereotyped as stubborn, ambitious, obsessional and perfectionistic, a view still held by some (e.g. Rubinowitz, 1973). Others, notably those with a psychiatric interest, have held that certain personality types directly cause migraine, particularly if associated with suppressed or repressed hostility, with the headache as a conversion symptom of guilt (Gainotti, Cianchetti and Taramelli, 1972; Menkes, 1974; Musaph, 1974). However, while evidence suggests that patients attending specialist clinics show higher levels of anxiety and other signs of neurosis than the general population (Selby and Lance, 1960; Hay, 1973; Merskey, 1975) such patients are a selected group and it is not necessarily true that the migrainous as a whole group are significantly different from the non-migrainous population (Friedman, 1975b; Nightingale, 1976).

An important study was carried out by Bille (1962) as part of his investigation of schoolchildren and it indicates children with migraine are more anxious than those without. He compared a group with pronounced migraine attacks with a group of normal children. The migraine children showed more symptoms of sleep disturbance, night terrors and temper tantrums and on self-description scales were more nervous, tense, anxious and fearful, a similar trend appearing in ratings by parents.

In a study by Henryk-Gutt and Rees (1973) an increase in neuroticism scores of the Eysenck Personality Inventory (EPI) was found firstly in 166 Migraine Clinic patients they studied and secondly in a group of migrainous Civil Servants. In addition the women but not the men, showed an increase in anxiety and somatisation scores on the Minnesota Multiphasic Personality Inventory (MMPI). However, both men and women showed increases in hostility scores on the Buss Scale and evidence of increased emotionality, in that migraine sufferers had significantly more psychological symptoms than controls.

Evidence of this nature, while it suggests a trend for migrainous individuals to show certain characteristics, does not imply causality, for as Barolin (1972) points out both could be caused by another factor. For the personality features to be causal a number of postulates would need to hold good.

1. there should be good agreement on the personality features involved. Apart from a trend towards anxiety and neuroticism, the agreement is not good (Harrison, 1975).

2. all person's exhibiting these personality features should have migraine. This is unsubstantiated, indeed Harrison (1975) comments "most headache groups describe themselves as more neurotic and more forgetful than do controls."
3. everyone with migraine should be anxious and neurotic. While there may be such a trend, there are many migrainous individuals who do not qualify for such labels.

As the evidence of a causal relationship is insufficient, most authors now reject that view, and instead support the view that, in people susceptible to migraine, psychological factors may predispose them to attacks (Rees, 1974; Harrison, 1975; Merskey, 1975; Speer, 1975; Nightingale, 1976; Pearce, 1977). The reasoning behind this view is illustrated by a quotation from Rees (1971).

"there is no specific personality type which is applicable to migraine in general. Many of the characteristics described ..... relate to traits of personality which in various ways are conducive to the development of tension: sensitiveness, over-anxiety and obsessionality are all traits which make the person respond to the environment and tend to produce emotional reactions which if bottled up or mounting in severity can act as precipitants of psychosomatic disorders."

Three additional explanations for the observed psychological differences have been made apart from the possibility of personality factors pre-disposing someone to migraine:-

1. Anxiety and neuroticism may be the consequence of chronic exposure to the risk of sudden pain (Harrison, 1975), or the consequence of that pain (Dalsgaard-Nielson, 1974). Blumenthal (1969) suggested, and Pozniak-Patewicz (1976) found, the majority of headache patients although voluntarily relaxed, showed continuous electrical activity in muscles of the head

and thought this "cephalgic" spasm was the consequence rather than the cause of headache. Such a situation might result in a diagnosis of "tense" and by implication "anxious".

2. the role of patienthood may play a part (Rees, 1974; Pearce, 1977). As Harrison (1975) points out pain can make one exceptionally irritable and patienthood can bring out the dependency needs in the best of us.
5. abnormalities or differences in body biochemistry or nervous systems may result in both the psychological trends and the migraine syndrome. Such a possibility seems likely and the evidence, given below, links in with underlying mechanisms proposed for other factors.

Valzelli (1972) presents evidence that in animals 'behavioural deviations' such as hyper-reactivity, irritability and also compulsive and repetitive aggressive outbursts are associated with a significantly depressed rate of amine turnover in the brain, especially of serotonin. Serotonin is a substance heavily implicated in the pathogenesis of migraine, as will be seen, and Valzelli's report provides grounds for speculation as regards personality features in humans. As will be shown later, a reduced serotonin turnover is consistent with an imbalance of hypothalamic functioning associated with dominance of the sympathetic nervous system. Such a dominance is consistent with the prodromal and early stages of a migraine attack, to be followed by a swing to parasympathetic dominance (Catino, 1965; Hall, 1971; Raffaelli and Menon, 1975). There is some evidence that the trend towards the higher neuroticism scores on the EPI shown by the migrainous may also be linked to the autonomic nervous system (ANS) and hypothalamus. As Henryk-Gutt and Rees (1975) point out, Eysenck (1967)

presents evidence that the neuroticism scores on the EPI are directly related to the degree of activation of hypothalamic centres and thus of the ANS response of the individual. They conclude that the high neuroticism scores are not the result of migraine, but of the raised level of reactivity to stress which may be a predisposing factor in the development of migraine in otherwise susceptible subjects. This raised level of reactivity to stress would thus directly explain the marked influence of emotional and mental stress as potent precipitators of migraine. As Morgan (1965) illustrates, the responses to a strong emotion, usually of rage or fear, tend to be those of sympathetic dominance. He also points out that some of the changes that take place in emotion also occur in response to other stresses such as overwork, prolonged exposure to cold and heat, severe burns or pain, and the 'ravages of disease', all of which have been noted as precipitants of migraine (see Tables 1.3 and 1.4).

The psychological precipitants are divided into 'emotional and mental stress' on the one hand and 'relaxation after stress' on the other. Sacks (1975) suggests relaxation after stress may produce a 'slump reaction' but gives no details as to how this causes migraine. A more convincing explanation emerges from the suggestion by Cameron (1974) that a high work load can act to inhibit overt feelings of anxiety until the work load has eased, and that in some cases the anxiety will then not reach its peak until after the crisis which originally gave rise to it has passed. This explanation means that release from stress, if accompanied by increased anxiety, should produce the symptoms of emotional stress and may also trigger migraine.

The role of depression is not discussed as the research findings on the biochemical changes accompanying depression remain somewhat controversial and a discussion of these is not directly relevant to this study.

Therapies regarded as particularly relevant to the above discussion are:-

1. psychiatric techniques, including psychotherapy. Results indicate this time-consuming and expensive method is limited in usefulness to a small number of patients. However, the majority of patients benefit from an explanation of the role of 'life stresses' and encouragement to reduce or avoid these where possible, while appropriate medication would also be prescribed (Boag, 1969; Barolin, 1972; Sacks, 1975; Rees, 1974; Speer, 1975; Sternbach and Delassio, 1977).
2. Another therapy may be interpreted as an attempt to break the vicious circle of migraine, pain, tension and over-arousal, migraine, etc. Blumenthal (1969) discusses the role of 'pain trigger points' in the head, neck and shoulders associated with spasm or contraction of muscles and advocated injection of these points with anaesthetic to relieve the pain and thus the tension, which Pozniak-Patewicz (1975) demonstrated to be a consequence of the pain. Hay (1976) reported this as a useful technique in the treatment of patients attending a Migraine Clinic.



3. Two other techniques may be seen as methods aimed at reducing muscular tension and of learning some measure of voluntary control over the ANS. The first technique is relaxation therapy, successfully used by Hay and Madders (1971) and the second is biofeedback which is more widely reported but seems to have varying degrees of success (Budzynski, 1973; Harris and Brady, 1973; Legalos, 1973; McDonagh and McGinnis, 1973; Sargent, Walters and Green, 1973; Wickramaskera, 1973; Koppman, McDonald and Kunzel, 1974; Hoffman, 1975; Reading and Mohr, 1976; Sternbach and Dalessio, 1977).

1.6.4 The search for common underlying mechanisms  
- (2) Physical exertion and fatigue

Bearing in mind the evidence given in section 1.6.3 on stress effects, physical exertion can be regarded as producing physiological stress. With regard to fatigue Cameron (1974) makes the interesting comment that fatigue is a concept which defies precise definition and that it is a useful label for a generalized response to stress over a period of time. Cameron also points out that if an individual becomes tired but is required to continue working, and especially if required to respond with greater effort, then they must put themselves under some stress to do so. Thus the mechanisms for stress produced migraine and related therapies discussed in section 1.6.3 are relevant here. An additional explanation is given by Dalessio (1974) for 'effort migraine'. He suggests that during intense physical effort altered levels of carbon dioxide in the blood would produce initial vasoconstriction and so enhance prodromal features, with the elevated blood pressure associated with muscular effort enhancing the headache.

In Table 1.4 the percentage of people reporting physical stress produced migraine is much lower than for mental or emotional stress migraine, except in the case of children. This could easily be explained in that adults are more able to avoid physical stress than emotional or mental stress, whereas the children Bille (1962) examined often reported school gymnastics and athletics sessions to be to blame and presumably they could not avoid these.



1.6.5      The search for common underlying mechanisms  
               - (3) Lack of food

It is agreed that migraine may be induced by hunger or missing a meal (Dalton, 1975) or on waking having not eaten for 12 hours or more (Rubinowitz, 1973; Pearce, 1976), but the underlying mechanism is still a matter of controversy. The alternative explanations are reviewed by Hockaday (1975). Early work inferred that an attack of migraine was likely to occur when blood sugar fell below a certain level and even recent literature lists hypoglycaemia among possible causes of migraine (Graham, 1969; Rubinowitz, 1973; Friedman, 1975b). However, research has indicated that a fall in blood sugar does not fully account for the precipitation of migraine (Pearce, Ron and De Silva, 1973; De Silva, Ron and Pearce, 1974; Byer and Dexter, 1975; Speer, 1975 and Pearce, 1976). Hockaday (1975) summarizes work on hypoglycaemia and also concludes that it is not proven that headache in hypoglycaemic states is related to the effects of glucose deprivation. She suggests that in such situations as exercise, prolonged sleep and lack of food that it is the absolute or relative shortage of carbohydrate supply (i.e. the threat of calorie depletion), which may be the important factor in the genesis of the attacks. She then proposes that the central threshold, or response, to this may be abnormal in some migrainous subjects, and one of the consequences of this may be a neurogenically determined attack. Hockaday then comments "The possibility of a state of chronic sympathetic nervous system over-activity with an appropriately low growth hormones response, is consistent with metabolic observations so far." Thus once again, over-activity of the sympathetic nervous system is implicated as an underlying mechanism producing migraine.

1.6.6      The search for common underlying mechanisms  
               - (4) Dietary factors

Food substances are thought to provoke attacks in some patients and as many as 25 per cent may report this (Selby and Lance, 1960; Hay, 1973; Arthur, 1974) but this is not a universal figure, some quoting lower figures (see Table 1.4) and Nightingale (1976) suggesting one-third. The foods listed as triggers include wines (especially red), sherry, yoghurt, cheese, chocolate, cola, eggs, pork, fish, Bovril, spices, fats, fried foods, oranges, tomatoes, pineapples, onions, legumes, apple, wheat, corn, coffee and nuts (Hanington, 1973; Hay, 1973; Ryan, 1974; Dalton, 1975; Speer, 1975; Nightingale, 1976; Pearce, 1976). Hanington and Harper (1968) in a study of 500 patients with dietary migraine found the cited foods were chocolate 75%, cheese and dairy products 48%, citrus fruits 30%, alcohol 25%, fatty fried food 18%, vegetables especially onions 18%, tea and coffee 14%, meat especially pork 14% and sea food 10%.

Pearce (1976) states " a good deal of dietetic idiosyncrasy is iatrogenic", that is resulting from the activity of physicians. To what extent migraine patients are intrinsically susceptible and to what extent they are influenced by their doctor, friends and the popular press is a difficult question to answer. The findings of Dalton (1975) suggest that while dietary factors may not be the only factor operating, they may be present prior to a migraine attack and yet not recognised as a precipitant by the sufferer. Using questionnaires she obtained data on food intake in the 24 hours prior to a spontaneous migraine attack in 2,313 cases and in the light of Hanington's work she examined these for the presence of the chocolate (33%), cheese (40%), citrus fruits (21%), alcohol (23%) and fasting

(67%). Some attacks involved more than one factor with only 5% having no dietary factor present. However, just 14% thought this reported attack was caused by food and 2% thought fasting to be responsible, while stress, worry, frustration and tension were frequently mentioned. The stage of the menstrual cycle was also important. Work by Hanington, Sandler, Youdim and their co-workers succeeded in implicating first tyramine (found particularly in substances which have undergone bacterial decomposition, e.g. yoghurt, cheese, game, smoked fish and some alcoholic drinks, e.g. red wine and port) and then beta-phenylethylamine (found in chocolate), which are vasoactive amines, in the production of migraine (Hanington, 1967; Hanington and Harper, 1968; Hanington, 1969; Sandler, Youdim, Southgate and Hanington, 1970; Hanington, Mullen, Kellow and Smith, 1971; Hanington, 1973; Sandler, Youdim and Hanington, 1974). These results have not been fully substantiated by other workers (Forsythe and Redmond, 1974; Moffett, Swash and Scott, 1974a, 1974b; Ryan, 1974; Schweitzer, Friedhoff and Schwartz, 1975; Ziegler, Hassanein and Ward, 1976; Ziegler and Stewart, 1977). In the double-blind placebo controlled studies by Moffett et al on chocolate and tyramine and by Ziegler and Stewart on tyramine, migraine occurred in some cases after placebo and not always after the incriminated substance. Unfortunately no data seems to have been collected by Ziegler and Stewart on other possible trigger factors that may have influenced the precipitation of migraine, although Moffett et al listed other factors their subjects found could contribute towards a migraine as stress, relaxation from stress, menstruation, fasting or changes in medication. Indeed the subjects of Ziegler and Stewart took their capsules in the morning "in a fasting condition" and it is unclear how long this fast continued, since lack of food can trigger migraine

(see Section 1.7), this might have affected the results in those susceptible to fasting. Indeed Ziegler and Stewart conclude "the possible interplay of multiple identifiable factors in the precipitation of migraine remains to be carefully investigated". Moffett et al concur by concluding "The development of frank migraine may thus be the result not of a single factor, such as chocolate, tyramine, stress or alcohol, but of several of these factors acting together in the susceptible individual".

Hanington, Mullen, Kellow and Smith (1971) suggested "that in dietary (tyramine) migraine, the patient suffers from a deficiency in the enzyme responsible for the sulphate conjugation of tyramine" and mention was also made of monoamine oxidase (MAO) enzymes. In later work Sandler, Youdim and Hanington (1974) showed a significant deficit of both phenylethylamine and tyramine oxidising ability by MAO (types A and B respectively). If the inactivation of these substances by the MAO enzymes is inadequate there are important implications, for they are both vasoactive amines and tyramine is a known noradrenaline (NA) releasing substance (Sicuteri, Del Bianco and Del Bene, 1972) and NA is a neurotransmitter in the sympathetic nervous system. In this connection, the following quotation from Sicuteri, Del Bianco and Del Bene (1972) is interesting since it ties together a number of the above points.



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In conclusion, the influence of dietary factors is not yet clear. Not only is more information needed on the metabolic route of tyramine and beta-phenylethylamine and on the enzymes and other factors involved in that route, but also on the interplay of dietary factors, both with other known precipitants and with the state of the internal environment in terms of humoral and neurogenic aspects including arousal states. For example, Youdim and Holzbauer (1976) note that progesterone can stimulate, and oestrogens inhibit, MAO activity but no studies were found investigating dietary (tyramine or beta-phenylethylamine) migraine in relation to stage of menstrual cycle and associated MAO activity. In addition, as Curzon and Hilton (1975) note there may be numerous dietary triggers but only fragmentary data on the concentration of amines in food-stuffs is at present available.

Despite the shortcomings of present knowledge, it emerges that yet another precipitant factor is associated with changes relating to the sympathetic nervous system, moreover, as will be shown later, the proposed lack of MAO is thought to affect serotonin turnover, a substance already mentioned in this search for common mechanisms in migraine.

1.6.7      The search for common underlying mechanisms  
               - (5) Hormonal factors

Greene (1969, 1975) considers the thyroid and pituitary are not directly involved, although evidence on the pancreas and the anomalies of carbohydrate metabolism in migraine is unclear. Greene notes that anxiety in dogs can produce water retention along the axis hypothalamus, posterior pituitary, renal tubules and knowing that anxiety or mental stress can precipitate migraine, wonders if such stress could thus account for the water retention which may precede migraine. The adrenal glands may be involved insofar as aldosterone regulates the salt and water content in the body causing water retention when present in excess. However, the base out of which all adrenal corticosteroids, including aldosterone, are formed is progesterone and fluctuations in this hormone are considered to be important in migraine.

The hormones oestrogen and progesterone are known to be important in the production of migraine attacks in women, and when authors mention hormonal precipitation of migraine they are usually referring to these hormones. In Section 1.5 it was shown that there was a higher incidence of migraine in post-pubertal females; this discrepancy may be accounted for by the influence of the menstrual cycle.

The complexities of the control of the menstrual cycle and its hormones will not be discussed here but are described by many authors including Morgan (1965); Dalton (1969); Harding and Thompson (1976).

Over several months migraine attacks in women may be seen at intervals which are roughly multiples of a fortnight. The times of risk being



at ovulation, and, principally, at pre-menstruation and the first days of menstruation (Dalton, 1973; Sacks, 1973; Epstein, Hockaday and Hockaday, 1975; Greene, 1969, 1975). Premenstrual headache may be exaggerated during the first three months of pregnancy and then absent until after the birth, although this is not universally true (Callaghan, 1968; Epstein, Hockaday and Hockaday, 1975). Oral contraceptives may exacerbate premenstrual and menstrual migraine, or, like pregnancy, result in the first attacks being manifested, yet in other women attacks may become less severe and less frequent (Carroll and Grant, 1975; Grant, 1974; Kudrow, 1975; Dalton, 1976). Both oestrogen therapy to correct hormone imbalance (Chaudhuri and Chaudhuri, 1975) and progesterone therapy (Greene, 1969; Dalton, 1975) being found beneficial in appropriate cases.

The exact roles of oestrogen, progesterone and other substances linked with the menstrual cycle remains unclear (Epstein, Hockaday and Hockaday, 1974; Hockaday, 1974; Horrobin, 1974a, 1974b; Nader, 1974; Nader, Tulloch, Blair, Vydelingum and Fraser, 1974; Epstein, Hockaday and Hockaday, 1975; Greene, 1975; Kudrow, 1975; Sommerville, 1975). Sommerville (1975) writes:

"Since men also suffer from migraine, such hormonal changes are likely to be of secondary rather than primary importance in the cause of the disorder, but their study as precipitating causes of attacks of headache may lead to a better understanding of the underlying cause of migraine."

Recent opinion agrees with this (Epstein, Hockaday and Hockaday, 1975; Greene, 1975) and Epstein et al suggest it may be possible to link the hormonal differences observed to abnormality in hypothalamic neurotransmitter mechanisms. In an earlier paper Hockaday (1974) had noted that oestrogens affect the metabolism of tryptophan, a precursor of

serotonin, and rates of serotonin turnover have already been mentioned in connection with migraine. Greene (1975) reviews the literature and concludes that future researchers will concentrate

"upon the effects of hormones on autonomic activity and on the actions of substances that influence this such as serotonin, the catecholamines and the enzymes that oppose them, and ..... other substances."

Thus, once again the ANS, monoamines, particularly serotonin, and enzymes, including MAO are thought to lie in the path from trigger factor to migraine attack.

#### 1.6.8      The search for common underlying mechanisms               - (6) Weather, heat and cold

Reference has been made to 'climatic conditions' (Duke-Elder, 1949), 'meteorological changes' (Friedman, 1975b) or more specifically glare and bright light, cold, heat, humidity and ionization of the atmosphere, and barometric pressure as factors inducing migraine. Several authors (Bille, 1962; Graham, 1969; Lance, 1973; Gomersall and Stuart, 1973; Sacks, 1973; Raffaelli and Menon, 1975; West, 1975) mention bright sunny days and the reflections of sun from sand, water, snow or metal objects as precipitants of migraine and the role of bright light and glaring reflections is considered in section 1.6.10. Excessive heat or cold are reported as triggers by a few authors (Bille, 1962; Graham, 1969; Sacks, 1973; Speer, 1975) and can be regarded as stress producing, as such the arguments in sections 1.6.3 and 1.6.4 regarding an underlying mechanism apply.

Surprising as it may seem, humidity with ionization of the atmosphere, may link into the emerging theme of serotonin metabolism. It is suggested (Gomersall and Stuart, 1973; Espadaler, Gimeno and Lage, 1974; Migraine Trust, 1975) that increase in severity of attacks is due not to the low humidity itself but to positive ionization of the air due to charged particles in the atmosphere, which if breathed in cause the release of serotonin. Such an explanation could account for not only migraine occurring in dry weather and in crowded, centrally-heated rooms but also for migraine attacks associated with certain winds and thunderstorms as these are preceded by ionization changes of the atmosphere.

Lance (1975) noted sudden changes in barometric pressure could induce migraine and rises in pressure seem the major problem (Engel, Ferris and Romano, 1945; Gomersall and Stuart, 1973) but no explanations for a causal mechanism were offered.

#### 1.6.9 The search for common underlying mechanisms - (7) Travel

Travel is of interest because on the one hand it relates to many of the preceeding factors and on the other hand it relates to certain aspects of visual stimulation. Although cited as a trigger factor (Bille, 1962; Sacks, 1973; Pearce, 1976) travel is not a unitary condition. Long distance travel in particular involves fatigue, especially for drivers; may involve anxiety; can result in meals being missed or foods not usually consumed being eaten, all of which are factors already discussed. In addition there are the factors of the motion of the vehicle; the rapid movement of the environment past car and train windows and the brightness and reflected dazzle

from the environment including incars at night, oncoming headlights.

Considering the incidence of motion sickness, Bille (1962) found it to be significantly higher (55 per cent) in a group of 75 children with pronounced migraine as compared with the control group (51 per cent) the significance of the difference ( $p < 0.01$ ) increased if only severe motion sickness was examined ( $p < 0.001$ ). The figure given by Pearce (1971, 1976) of 60 per cent of his migraine patients agrees well with Bille's figure. However, only 15 per cent of Bille's pronounced migraine group reported motion sickness as inducing migraine. Sacks (1975) comments on the role of passive motion, saying it is normally soothing and soporific, but that in some

"the response to passive motion (or direct vestibular stimulation) is inordinate and intolerable - such people may suffer from intense 'motion-sickness' ..... (with nausea, vomiting, pallor, cold sweating, etc.) .....; if vascular headache is present in addition to the above symptoms, a motion migraine will result" (p. 154).

Sacks feels that it is important to note that passivity and passive stimulation are essential in these reactions for many patients extravagantly prone to motion-sickness are perfectly able to drive their own cars, or pilot their own boats and planes. This comment is interesting since according to the Migraine Trust (1975) it is unclear whether the high incidence of motion-sickness in the migrainous results from an excessive response to stimulation of the balance mechanism in the ear. The doubt arises

"since a form of motion-sickness can be induced in certain individuals by movement of the environment alone in the absence of bodily movement as for example with a wide angle cinema screen a particular susceptibility among migraine sufferers to this kind of stimulation cannot be ruled out." (p.31).

Thus an alternative (or additional) explanation for the relative immunity of drivers, as opposed to passengers, might be that drivers tend to look forwards rather than sideways and so reduce the effect of rapid movement past the eyes. A suggestion substantiated by Bille (1962) who found many of the pronounced migraine children were affected by looking out of a train window and seeing telegraph poles and fences go by. Maybe children suffer less from severe motion-sickness as they grow older because, being taller, they can then see forwards over the front seats instead of being forced to look out of the side window, and being able to see forwards would also account for the 'I'm alright if I sit in the front passenger seat' syndrome.

1.6.10     The search for common underlying mechanisms  
               - (8) Visual factors

When this research was commenced in 1973 much of the work on trigger factors discussed earlier in this chapter had yet to be published. At the present time a common pattern seems to be emerging from studies of the precipitant factors in that many are associated with an over-active sympathetic nervous system and tie into the 'serotonin theory'. (This theory and its implications for this study are considered in section 1.7). However, the only suggestion that might link visual precipitants of migraine into this picture was recently made by Herberg (1975), who suggests bright light may act by inhibiting the synthesis of pineal melatonin, a derivative of serotonin which is able to raise the serotonin content of the midbrain. The relevance of this suggestion is shown in section 1.7.

When considering visual factors and migraine authors have

- (a) considered the condition of the eye itself
- (b) reported the types of visual stimuli triggering migraine
- (c) examined the electroencephalographic responses to photic stimulation (considered in section 1.10).

Literature on the condition of the eye was studied to check whether this is relevant to the study and that on visual stimuli with a view to preparing a questionnaire on visual precipitants to be used in structured interviews (as mentioned previously).

Conditions relating to the eye itself will be considered first.

Headaches may occur in organic diseases of the eye such as herpes zoster ophthalmicus, and glaucoma (Heyck, 1969; Lyle, 1969; Behrens, 1976). In glaucoma the pain may radiate over the side of the head and be extremely severe in nature, even resulting in reflex vomiting and as Heyck points out may be mistaken for migraine in some circumstances. Headaches may also occur in conditions affecting organically healthy eyes such as squint (latent, intermittent or manifest), heterophoria and refractive errors (Heyck, 1969; Lyle, 1969; Behrens, 1976). It is errors of refraction that have been associated with migraine. In 1934 Turville, an ophthalmologist, wrote "a high percentage of sufferers have been completely relieved of the distressing recurrence of migraine headaches by suitable optical treatment." Fifteen years later Duke-Elder (1949) was to express his view and wrote as follows:

"Refractive errors are usually cited as a common adjuvant cause, some authors considering eyestrain of fundamental importance and its correction by spectacles a specific cure, others assessing it as of little importance. The truth is probably a mean between the two. Eyestrain almost certainly acts as a common source of mental and reflex exhaustion and thus may precipitate and worsen attacks: spectacles may relieve the paroxysms and only rarely abolishes them, and their influence is perhaps best regarded as relieving strain equally with other factors, which, acting singly or in combination, may prepare the way for the development of an attack."

Certainly errors of refraction continue to be mentioned (Dille, 1962, 1969; Speer, 1975) and Duke-Elder's view seems to express recent thinking, with several authors (Dille, 1962, 1969; Heyck, 1969; Lyle, 1969; Behrens, 1976) pointing to the need for an uncorrected or inadequately corrected refractory abnormality to be attended to.

Considering next the various visual stimuli implicated as triggers these could be loosely grouped as dim light, bright light, glare and flicker, and, finally, pattern.

Poor illumination is cited by Turville (1954), who quotes it from an earlier paper by Critchley and Ferguson, and by Speer (1975), but they offer no explanation. However, Lyle (1969) states "considerable headache may result if illumination is insufficient for the task in hand as may occur in some offices or factories" but he does not necessarily implicate migraine. Dim light will therefore not be considered further.

The term 'bright light' is used by many authors when listing trigger factors (Walsh, 1957; Graham, 1969; Lance, 1973; Rubinowitz, 1973; Sacks, 1973; Arthur, 1974; Friedman, 1975b; Migraine Trust, 1975; Raffaelli and Menon, 1975; Wakefield, 1975; West, 1975; Pearce, 1976; Damassio, 1977), but it is generally unclear whether they are referring to direct bright light only or to a combination of direct and reflected light. Bright sunlight is explicitly mentioned by Graham (1969); listed by the Migraine Trust (1975); cited as affecting 30% of Arthur's (1974) sample studied in New Zealand, and mentioned by West (1975). Bright artificial light is given as a trigger by Sacks (1973) and West (1975) as well as in the 1971 Focus on Migraine list

(which is given in Table 1.1), and Turville (1954) quotes one case who could always precipitate an attack by gazing into a naked paraffin lamp.

An interesting comment is made by the Migraine Trust (1975) about the distinction between glare and bright direct light.

"The first condition, which is well known as a precipitant, is glare. Bright dazzling light can be particularly irritating during an attack, but many people report it as inducing migraine. It is not strong sunlight in itself which is the main culprit, but dazzling reflected light, such as that which shines through white clouds, or shimmers back from the surface of snow or water. Watching a badly adjusted television, or speaking to a friend who is seated in front of a brightly lit window can have the same effect." (p. 25-26).

One assumes the "badly-adjusted television" had its brightness or contrast badly set.

Moreover glare and flicker may be spoken of together as is illustrated in Table 1.5, and both may sometimes operate in the same situation, e.g. television or cinema. The term flicker seems to be used to cover regular, irregular and single flashes, e.g. television, strobe lighting, oncoming headlights or a flashbulb.

Referring to Table 1.5 it can be seen that no clear picture emerges as to the incidence of visual stimuli inducing migraine in the migrainous population as a whole, partly because the majority of studies are on patients (see discussion of epidemiology in Section 1.5) and partly because the terms used vary from the general "bright light" of Pearce (1976) to the specific divisions of Bille (1962) and Arthur (1974). Children appear more prone to have attacks induced by visual stimuli than adults, with 84% of children being reported as affected by Bille (1962), and between 24% (Hay, 1973) and 47% (Selby



TABLE 1.5 Authors reporting incidence of visual stimuli inducing migraine.

Author	Sample	Results
Selby and Lance, 1960	300 female patients 200 male patients (Australia)	293 (47% reported glare as a precipitant, including those who experienced attacks after exposure to flicker of moving pictures or T.V.
Bille, 1962	41 girls and 32 boys aged 9 to 15 years with pronounced migraine, from 8993 schoolchildren (Sweden)	84% affected by "stroboscopic effects" which included (a) 36% sitting "too near in cinemas or in front of television". (b) 14% affected by "sun reflections from sea or snow". (c) 34% affected by "both cinema or T.V. and sub-reflections".
Pearce, 1971, 1976	450 patients attending Headache Clinic (England)	30% were affected by "bright light".
Gomersall and Stuart, 1973	56 volunteer migrainous subjects (Scotland)	The hours of sunlight did not affect the number of attacks observed on a particular day. But, when divided into mild, moderate and severe attacks, on days with more than 2 hours of sunshine there was a 1.2 times greater percentage of severe attacks (p 0.05). Snowcover and its resultant dazzle indicated a significant association between dazzle and severity (p 0.01).

TABLE 1.5 CONT'D.

Author	Sample	Results
Hay, 1973	177 female patients 67 male patients (England)	24% reported excessive sensory stimuli "usually glare and flicker" as precipitants
Arthur, 1974	67 female patients 35 male patients (New Zealand)	"Sunlight" affected 20% of the men, 36% of the women and 30% of the total number. "Glare, shimmering light" affected 9% of the men, 18% of the women and 15% of the total. "Eyestrain, films, T.V." reported as affecting 5% of the total.

and Lance, 1960) being reported as overall figures, with Arthur's (1974) separate figures not necessarily being additive. The results of Gomersall and Stuart (1975) while not strictly population incidence figures do add support to the role of sunlight and sun on snow in the production of migraine.

Situations involving "bright light" as a precipitant were mentioned earlier and those for glare are given below. Some authors mention only glare or shimmering light (Turville, 1934; Selby and Lance, 1960; Hay, 1973; Speer, 1975; Nightingale, 1976; Pearce, 1976), while others give specific examples (see Table 1.6). None of the authors go into details apart from Gomersall and Stuart (1975) whose results are summarized in Table 1.5. However, Graham (1969), West (1975) and Pearce (1975) mention that bright light or glare can precipitate a visual aura followed by a classical attack, within seconds or minutes if it is a strong sudden stimulus. Such a quick reaction is suggestive of a neurogenic rather than a humoral mechanism.

Situations in which flickering light gives rise to migraine are given as examples by most authors (see Table 1.7) although Damassio (1977) does not do so. Authors have made additional comments, particularly about television (T.V.) and cinema. Hay (1968) suggested the rate of flicker might be important as patients were more upset by that of cinema screens than by that of T.V. However, while the flicker of cinema screens is at 50Hz and the predominate rate of T.V. screens in this country is at 50Hz, T.V. screens can also have a 25Hz component in the flicker (Jeavons and Harding, 1975). Such an overlap raises a query as to whether the rate of flicker is the only factor in cinema and television viewing. Bille (1962) dismissed suggestions that

TABLE 1.6 Specific situations involving glare which may precipitate migraine, and the authors citing them.

<u>Situation</u>	<u>Authors</u>
Sun reflections:-	
rippling water or sea	Bille (1962, 1969)
at the beach	Lance (1973); Sacks (1973).
snow	Bille (1962, 1969); Gomersall and Stuart (1973); Migraine Trust (1975); West (1975).
paper	West (1975)
chrome trim of car	West (1975)
Microscopy	Critchley and Ferguson in Turville (1954); Rubinowitz (1973).
Facing bright windows	Migraine Trust (1975)
Fluorescent light	Focus on Migraine 1971 list (see Table 1.1)

Note: Fluorescent tubes when working correctly emit a fluctuating light but few people seem to be aware of this, but once the tubes become faulty and a noticeable fluctuation of flicker occurs people may react differently. This is discussed in Section 2.

TABLE 1.7      Specific situations involving flicker which may precipitate migraine, and the authors citing them.

<u>Situation</u>	<u>Authors</u>
Television	Selby and Lance (1960); Bille (1962, 1969); Hay (1968); Focus on Migraine list (see Table 1.1); Lance (1975); Rubinowitz (1973); Sacks (1973); Arthur (1974); Nightingale (1976).
Faulty or badly adjusted T.V.	Friedman (1975b)
Cinema	Critchley and Ferguson in Turville (1934); Selby and Lance (1960); Bille (1962, 1969); Hay (1968); Focus on Migraine list (see Table 1.1); Lance (1975); Rubinowitz (1973); Sacks (1973); Arthur (1974); Nightingale (1976).
Faulty fluorescent light	Migraine Trust (1975)
Lighting in vehicular tunnels	Hay (personal communication, 1973)
Flashlights	West (1975)
Headlights	West (1975)
Stroboscope	Bille (1962)
Travelling past	
railings	Turville (1934)
telegraph poles and fences (train)	Bille (1962, 1969)

program content could be an exciting factor due to the "stimulation of unconscious fantasy rather than to visual fatigue", since none of the children mentioned anxiety or worry about what they had seen. However, the children often mentioned they could prevent an attack by not sitting too near the cinema screen or by having a lamp lit in the television room. Both measures would reduce the stroboscopic irritation, the one by reducing the area on the retina affected and the other by reducing percentage fluctuation of light. This, however, does not exclude the possibility that in the cinema the experience of movement of the environment alone, as discussed in section 1.6.9 in connection with motion sickness, might be the important factor and this, too, would be reduced by sitting further away. How much this latter would operate in television viewing is unclear.

When discussing the experience of movement of the environment alone as a trigger of migraine, the examples were given of rapid movement past railings, and, when travelling by train, past telegraph poles, both these situations would also involve flicker on occasions when the sun was shining through them. A further situation where both factors may operate exists in the series of vehicular tunnels found in Birmingham, which Hay mentioned in a personal communication in 1973. One patient in particular found that an attack would often follow whenever she drove through them, especially if they were long. In addition to the rapid movement past the tunnel's walls, the centre section of long tunnels is lit, not by a continuous line of fluorescent strips, but by spaced lights which create a flicker effect as one drives through.

The only suggestions for possible mechanisms linking visual stimuli to migraine are that such stimulation causes excessive arousal, (Sacks, 1973) and the Migraine Trust (1975) refer to the research indicating that

"..... some people have certain cells in their brain, which are more excitable than in other people in their response to light ..... intermittent flashes at a rate of 14 to 16 per second were shown to produce the highest response, which can account for the particularly noxious effects of a dazzling flicker."

Unfortunately the source of this information is not given but the findings of a number of studies relating to this (Golla and Winter, 1959; Bille, 1962; Smyth and Winter, 1964; Townsend, 1967) are considered later in section 1.10 and appear to support the hypothesis of an enhanced response at certain rates.

The possible role of pattern is rarely considered. Speer (1975) quotes from a 1904 publication of Gould which indicates migraine can be triggered by

"..... looking at striped wall paper or a striped dress or trellis. One of my patients has a life-long intolerance to striped wall paper, Venetian blinds, dresses with strong patterns ....."

More recently Williams (1972) wrote to "The Lancet",

"Many lorries now have strips of red and yellow diagonal fluorescent paint on their rear tail boards ..... I (and I know many others) find this pattern very painful to look at, and, if I stare at it for long, it gives me a form of migraine."

No suggestions are made by these authors as to causative mechanisms.

With regard to situation specific therapy, Gomersall and Stuart (1973) suggest the avoidance of dazzle by the use of tinted spectacles. However, it should be noted that tinted lenses merely reduce the quantity of incoming light to which the eye rapidly adapts, and that to cut out reflected light (dazzle) polarized lenses are required,

these being specifically recommended by the Migraine Trust (1975).

The general view is best summarized by Bille (1969).

"If the provoking factor is of an optical nature then the treatment should consist of its modification or, as far as possible, its exclusion. Television viewing should be reduced, or at least there should be a lamp lit in the room. The use of sun-glasses to counter-act sun reflections on snow and water, avoidance of looking out of the window on train journeys, etc., may also be beneficial. The "(individual)" with a refraction error should have this corrected."

Thus points arising from the literature indicated

- (a) Conditions of the eye did not directly cause migraine.
- (b) Other than bright light or glare, a number of specific situations have been reported as triggering migraine, these include watching cinema or T.V., fluorescent lighting, travelling through vehicular tunnels, oncoming headlights, stroboscopes and certain patterns. Because much of this evidence was derived from reports of individual cases no assessment of their relative importance could be made and this was taken into account when planning the questionnaire on visual stimuli (see Section 2.1.5).



## 1.7 Pathogenesis of Migraine

In the last forty years there has been an increasingly intensive search for vascular, chemical and electrical disturbances occurring in relation to migraine attacks and a proliferation of theories on the mechanisms involved in the causation of attacks. The huge mass of literature has been summarized by various authors (Wolff, 1963; Hanington, 1973; Lance, 1973; Sacks, 1973; Pearce, 1975). These works and other references were examined with the intention of extracting a survey of current thinking, with the emphasis on those aspects which might explain observed electroencephalographic and evoked potential changes between attacks, as opposed to those attributable to vasoconstriction, with resultant ischemia or edema, and associated lack of oxygen during an attack (see section 1.4.6). Early theories on pain production only partly explain the pain of migraine and are examined to expose this insufficiency. Current thinking on pain is then related to migraine. This thinking involves central as well as peripheral aspects in pain and is consistent with observations of the involvement of the limbic system in migraine especially the hypothalamus and its associated ANS functions.

### 1.7.1 The mechanisms of pain production in migraine headache - early hypotheses

The pain of migraine was long thought to be of vascular origin because of the observation that arteries and veins were prominent in the forehead and temples during the attack and that pressure over the scalp vessels or common carotid artery in the neck eased the pain to some extent (Wolff, 1963; Lance, 1973). Wolff was able to show, in a variety of ways, that the intensity of migraine headache is closely proportional to the dilation of extracranial arteries, but this

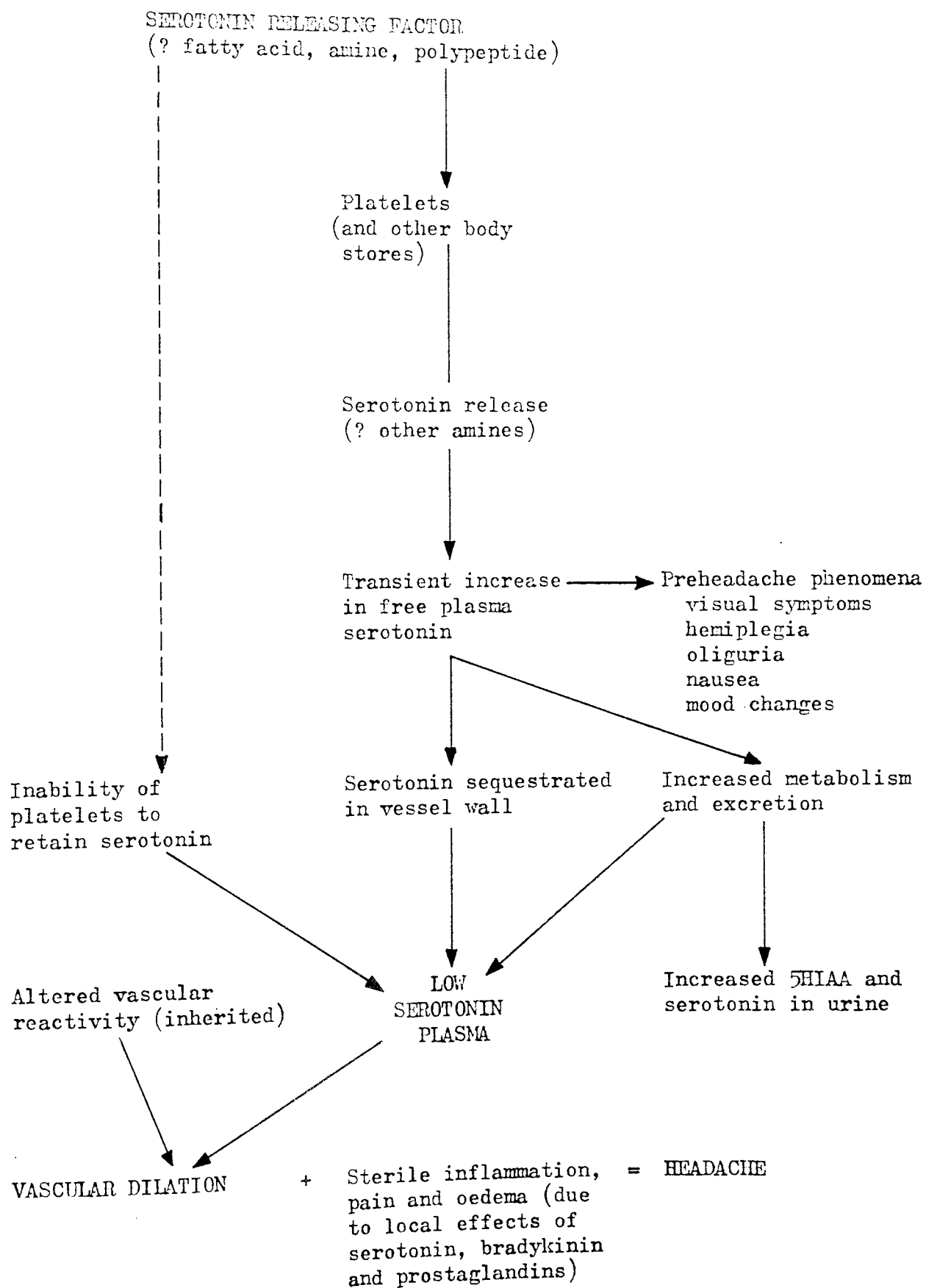
dilation is not sufficient in itself to cause the pain, since normal persons do not experience headache after strenuous exercise, or a hot shower or bath, which cause obvious dilation of the scalp arteries. One suggestion (Lance, 1973) is that there is imbalance between the calibre of large and small vessels during migraine with the dilation of the capillaries not keeping pace with the dilation of the arteries, so that the vessel wall becomes over-extended. The concept is supported by the appearance of most patients who look pale during migraine headache despite pounding temporal vessels. It is hard to reconcile this with tissue clearance studies which indicate there is increased blood flow in the fronto-temporal region during migraine especially on the headache side. It is possible that shunting of blood may take place deep to the constricted skin capillaries, thus removing the injected isotope rapidly while maintaining an increased pressure in the major arteries. Heyck (1970) found evidence of abnormal arterio-venous shunts and suggested such shunts cause higher arterial pressure and an increase in pulse amplitude which would subject the sensitive thin-walled arterioles to severe distension stress. Such pain is intensified by the accumulation around the dilated arteries of various substances which are pain-sensitizing. The polypeptide bradykinin is produced by damaged tissues during the course of inflammation and swelling, is destroyed by enzymes released by the body and produces severe pain when injected under the skin or into the deeper tissues of the body (Wolff, 1963; Lance, 1973; Melzack, 1973; Fanchamps, 1975). Lance (1973) suggests the local release of heparin and histamine from mast and basophil cells may be associated with the accumulation of kinins in the vessel wall, and possibly with the local action of serotonin (5-hydroxytryptamine, 5-HT) in the production of pain from distended arteries during migraine.

### 1.7.2 The role of serotonin (5-HT) in migraine

Considerable work has been carried out on serotonin and its possible role in migraine (Lance, Anthony, Hinterberger, 1970; Cumings, 1971; Curzon, 1972; Sacks, 1975; Sicuteri, Anselmi and Fanciullaci, 1974; Anthony and Lance, 1975). Following consideration of research findings Anthony and Lance (1975) put forward a hypothesis, which is summarized below, with an accompanying diagram reproduced in Fig. 1.2. They suggest that a serotonin releasing factor (yet to be identified), appears in the blood at the onset of the attack, and this leads to the sudden discharge of serotonin from storage sites, including the platelets, with consequent increase of serotonin levels in the blood. This increase could produce vascular constriction, and in intracranial vessels vasoconstriction could be responsible for the mood changes and possibly the other neurological preheadache features. As the released serotonin is excreted or metabolised, its blood levels fall rapidly and so its vasotonic influence decreases with resultant vasodilation of the scalp vessels and constriction of skin capillaries. Fluctuations in plasma serotonin during the attack could stimulate the vomiting centre in the medulla and cause the nausea and vomiting so frequently present. The activity of the serotonin releasing factor would keep blood levels of serotonin low by preventing platelets from taking up serotonin from the gut, and the reduced serotonin content of the platelets during migraine has been confirmed. While blood levels of serotonin remain low so does the loss of vascular tone. As the activity or amount of the serotonin releasing factor is expended, a corresponding rise of plasma serotonin terminates the attack. Lance and Anthony end their statement as follows:-

FIG. 1.2

Reproduction of a diagram presented by Anthony and Lance (1975) as part of the hypothesis on the role of serotonin in migraine (see text).



"Pain and oedema of arterial walls, which are responsible for the headache, could be due to the irritant action of released serotonin on arterial nociceptors, or due to local release of prostaglandins or bradykinin, both of which are known to produce vasodilation and headache in man."

This hypothesis receives support from the observations made by the authors listed above, but is insufficient to comprise a complete explanation of the phenomena of migraine, notably the pain, as will be shown later.

Anthony and Lance (1975) make some speculations about the nature of the serotonin releasing factor, and consider two groups of possible factors. As these tie in with some of the precipitant factors considered in section 1.6, these possible serotonin releasing factors will be briefly considered. Firstly there are certain free fatty acids (FFA), especially stearic, palmitic and behenic, which are known to be potent releasers of platelet serotonin, whose molecular size fits other experimental data on a possible serotonin releasing substance. Hockaday (1975) refers to earlier work published in 1971 that patients who have their attacks triggered by fasting, show a two to three-fold increase in FFA during headache as opposed to those who do not develop headache following fasting. Moreover the difference in FFA levels was seen before the onset of headache, suggesting the rise in FFA is an associated abnormality even if it is not involved in causation. Hay (1973) found fatty foods to be a precipitating factor but there appears to be no published work on the role of fat in the diet.

To diverge slightly, prostaglandins, mentioned earlier with regard to pain-sensitization are themselves long chain unsaturated fatty acids.

These vasoactive substances produce skin flushing if given by intravenous infusion, which is at variance to the appearance of most sufferers during migraine (Anthony and Lance, 1975) but while these substances may not be a primary factor they may be a secondary factor in the production of vasodilation and headache. Serotonin, as already noted, can release or activate prostaglandins (Anthony and Lance, 1975) and Sandler (1972) commented that the liberation of prostaglandins by the hormonal changes at the end of the menstrual cycle (a time women are more susceptible to migraine), could play a role in the course of menstrual migraine. The path of these hormonal changes seems to be that the drop in progesterone, and thus the relative increase in oestrogens results in decreased monoamine (MAO) activity (Belmaker, Murphy, Wyatt and Loriaux (1974) which could, as is discussed below, result in a release of serotonin and, in turn, prostaglandins. Sandler (1972) also suggested that tyramine, in those sensitive to it, could be responsible for the release of prostaglandins.

This mention of tyramine both ends the divergence from the main theme and links us to the other groups of possible serotonin-releasing factors considered by Anthony and Lance (1975), which are tyramine and phenylethylamine, both of which were mentioned in section 1.8.1 in connection with dietary triggers. Data on phenylethylamine is limited and consideration is therefore concentrated on tyramine. Sandler, Youdim, Southgate and Hanington (1970) proposed that tyramine produced migraine attacks by virtue of the fact that the substance could enter the circulation in sufficient amounts to release other amines, and that this was due to defective amine-inactivating mechanisms in these tyramine-sensitive subjects. They demonstrated both a defect in platelet-MAO activity during migraine, a finding repeated later (Glover, Sandler, Grant, Rose, Orton, Wilkinson and Stevens, 1977),

as well as a conjugation defect involved in the inactivation of tyramine. Sicuteri, Buffoni, Anselmi and Del Bianco (1972) showed that such enzyme activity is lower and more variable in migrainous patients compared with controls both during and outside an attack and Sandler, Youdim and Hanington (1974) also recorded a significant decrease outside an attack as compared with controls. Investigations indicated that MAO could be separated into two (and possibly more) types on the basis of their preferential activity with different amine substrates (Sandler, Youdim and Hanington, 1974; Glover et al, 1977). MAO A is specific for 5-HT and noradrenaline (NA); whereas for MAO B the preferred substrate is phenylethylamine, but tyramine and dopamine are substrates for both the A and B forms. Studies by Sandler (1972) and Sicuteri, Buffoni, Anselmi and Del Bianco (1972) suggest it is the B type MAO that is deficient in migraine. However, Glover et al (1977) point out that although human platelets have been used extensively to provide an index of MAO activity in general, they appear to contain only type B of the enzyme. Therefore it is not necessarily only MAO B which is deficient.

In 1974 an editorial in the Lancet concluded migraine was caused by "a specific biochemical deficiency which allows certain vasoactive amines to accumulate instead of being oxidased, and that when these reach a critical level they precipitate an attack." More recently, Sandler (1977) has refined and criticised such an approach, for on the one hand he notes that migraineurs examined during attacks showed lower MAO activity than controls, while activity in the attack free periods, although lower, was not significantly so. On the other hand he comments:

"The cause of the temporary decrease in platelet MAO activity during an attack is unknown. Whether the decrease contributes to the attack, results from it, or is caused independently by some other factor, e.g. an associated hormonal imbalance, has not been decided."

Doubts about the completeness of explaining migraine in terms of serotonin action and an MAO deficiency have been expressed (Bruyn, 1976; Ziegler, Hassanein and Ward, 1976), both on the grounds that abnormalities of MAO can be found in other conditions including depression and schizophrenia, and because artificial lowering of serotonin levels by reserpine will induce a dull, bilateral headache in normal subjects, but not the paroxysms of migraine, even though as Welch, Gaudet, Wang and Chabi (1977) point out there is evidence that the serotonergic system has an inhibitory influence on central perception of pain, with a fall in serotonin causing an increase in pain sensitivity, (it was earlier noted such a fall accompanies the migraine headache). This point is also made by others (Sicuteri, Anselmi and Fanciullacci, 1974; Appenzeller, 1975), indeed Sicuteri and his co-workers felt that a lowering of the pain threshold was a necessary part of the explanation of migraine and Sicuteri (1976) wrote that their present theoretical assumption is "that pain in migraine headache is central in origin, and is due to a disorder of the integration, modulation, and inhibition of pain-related structures in the brain stem" with this disorder related to derangement of neurotransmitter turnover, particularly of serotonin.

### 1.7.3 Central pain perception and its implications for migraine

In 1965 Melzack and Wall proposed the now widely accepted gate-control theory of pain (Melzack, 1973; Hannington-Kiff, 1974). According to this hypothesis the output of a group of first central transmission (T) cells in the posterior horn depends upon a balance of activity



which plays upon them and which originates in large and small afferent fibres of the posterior roots. If the small fibre activity is dominant, there will be presynaptic facilitation and an increase in T cell activity; this results in pain (the gate is open). On the other hand, if large fibre activity is dominant pain is not perceived (the gate is closed). This hypothesis assumes that the number of impulses reaching appropriate parts of the brain in a given time determine the occurrence of pain. More recently there has been the suggestion that 'opening' or 'shutting' of the gate can be facilitated 'from the inside', that is centrally, and so alter pain thresholds (Melzack, 1973; Hannington-Kiff, 1974; Fields and Raskin, 1976). Any interference with normal inhibitory inputs, central or peripheral, could be expected to increase excitability of these pain-transmitting neurons and produce either spontaneous pain or hypersensitivity.

Earlier the role of pain-sensitizing substances was mentioned, and this peripheral facilitation can be blocked by aspirin, if taken early enough in a migraine attack, for it acts peripherally by interfering with the synthesis of prostaglandins and by blocking the effects of bradykinin (Hannington-Kiff, 1974). Unfortunately aspirin seldom obliterates the pain of migraine, although it can reduce it.

Among the drugs known to act centrally certain anticonvulsants have been found effective in migraine. Fields and Raskin (1976) found the efficacy of phenytoin (known to act as an anti-convulsant) in treating migraine was unrelated to epileptogenic activity and when administered intravenously transiently improved the large majority of patients so treated. They commented that anticonvulsants seemed most effective against pain arising from dysfunction of the nervous system. Their

rationale being that

".... the actions of phenytoin on the nerve membrane would be expected to reduce repetitive firing of neurons. If pathological hyperactivity depends on neuronal membrane instability leading to repetitive discharge, phenytoin and other anticonvulsants that have a similar mode of action might act by stabilizing the membrane."

They note that such anticonvulsants seem to be effective whatever the cause of neuronal hyperexcitability in epilepsy and/or pathological pain states.

The suggestion of repetitive discharge finds an echo in the paper by Appenzeller (1975), who suggests "that reduced serotonin turnover related to deficient MAO in the brain leads to an increase of spontaneous firing rates of raphe neurons," like the later report of Welch, Gaudet, Wang and Chabi (1977). Appenzeller notes that depletion of serotonin from the brain increases the response to painful stimuli and thus the serotonergic system appears to act as an inhibitory influence. He also states that the raphe system has the largest number of serotonin containing neurons in the brain. Koella (1977) enlarges on this as follows:

"..... brain 5-HT is bound to the neurons whose perikaria reside in the raphe nuclei of the lower brain-stem and whose axons project rostrally to the diencephalon, basal forebrain, the basal ganglia, the limbic system and the neocortex ..... adrenergic systems originating particularly in the area of the locus coeruleus of the pons have been demonstrated, and recent physiological experiments suggest that there are cross-links between the serotonergic and the adrenergic ascending systems ..... (with) an essentially antagonistic role for noradrenaline and serotonin."

#### 1.7.4 The involvement of the hypothalamus

In the literature reviewed it is unclear to what extent derangement in the functioning of these raphe neurons would account not only for a decreased pain threshold but also for imbalances noted in the ANS

functioning in connection with migraine, the role of noradrenaline in migraine, and the central hyperexcitability postulated in connection with some observations on migraine.

Noradrenaline acts as a neurotransmitter in the peripheral sympathetic nervous system (SNS) as well as a central transmitter. The role of the SNS in central pain perception is unclear but sympathetic nerve block can relieve a significant number of pains in which there is no obvious autonomic involvement, presumably affecting regional gate control. However, a nerve block with a local anaesthetic will occasionally produce relief from chronic pain which outlasts the usual length of action of the agent and sometimes relief is permanent (Hannington-Kiff, 1974), the explanation for this is not certain but one possibility is an alteration at central level, although alterations at the peripheral level, including facilitation by relaxation of muscles previously tensed by pain response, may also be involved. This observation is relevant to migraine for Hannington-Kiff (1974) observed that many people with migraine complain of focusing difficulties before the onset of the headache and that since focusing of the eyes is under autonomic control, it is possible the first change to occur in migraine is in the A.N.S. Moreover Hay (1976) observed that following injection of pain trigger areas with local anaesthetic visual disturbances, both blurring of vision and classical visual aura, were relieved and attacks aborted.

In this connection two further observations are of interest. Firstly, when discussing anomalies of carbohydrate metabolism Hockaday (1975) concluded that the possibility of a state of chronic sympathetic nervous system over-activity, with an appropriately low growth hormone

response, would be consistent with metabolic observations so far. Secondly, Hannington-Kiff (1974) links hunger with focusing difficulties which, as mentioned above, may be a migraine aura. Hannington-Kiff found the monocular near-point of accommodation was generally more distant before than after food in a group of subjects who had regular headaches, in contrast to the control group in whom there was little or no such change, the difference between the two groups being highly significant. Hannington-Kiff suggested that in subjects with regular headaches the autonomic nervous system in the face is more labile in relation to hunger, and that hunger might produce these effects by altering the activity of the hypothalamus.

The hypothalamus is regarded as the control centre of the A.N.S. (Smith, 1970) and suggestions about its involvement in migraine have a long history for Speer (1975) quotes from authors writing in 1883 and 1885 who noted S.N.S. over-activity in migraine patients. More recently authors mentioning S.N.S. over-activity in migraine, particularly leading up to an attack and in its early stages, have included Catino (1965); Leon-Sotomayor, (1974); Hockaday, (1975) and Speer, (1975) and mention was also made earlier in Section 1.6 on precipitants. A greater number have implicated the A.N.S. as a whole or specifically invoked the hypothalamus (Friedman, 1970, 1975a; Hall, 1971; Sacks, 1973; Dalsgaard-Nielson, 1974; Hannington-Kiff, 1974; Appenzeller, 1975; Greene, 1975; Herberg, 1967; Hockaday, 1975; Mersky, 1975; Bruyn, 1976) and some have suggested a wider involvement of the hypothalamus and its adjacent brain areas (Herberg, 1975) or specifically the limbic system (Raffaelli and Menon, 1975).

In 1970 Friedman wrote:

"Certain features of the migraine syndrome such as vasomotor changes and the reversal in character of the accompanying autonomic signs and symptoms including appetite, fluid intake, sleep, and mood changes, suggest that the hypothalamus plays a role in the migraine attack. Most of these features appear to represent either inhibition or activation of the hypothalamic centre."

This view is enlarged on by Herberg (1975) in the most recent review of the hypothalamus and aminergic pathways in migraine, where not only are the symptoms considered but also the precipitating factors, e.g. the so-called 'migraine personality' and excessive lateral hypothalamic activity.

#### 1.7.5 Implications for this study

If one accepts the preceding evidence and assumptions then one would expect the migrainous individual to have a permanent deficit of one or more types of MAO and that various factors known to influence brain monoamine turnover, such as ovulation, menstruation, pregnancy, stresses, aggression, depression, sleep deprivation and fever (Greene, 1975; Sicuteri, 1976; Youdim and Holzbauer, 1976; Sandler, 1977) would either exacerbate or relieve the effects of this deficit. The effects include the rate of serotonin turnover in the raphe neurons, which in turn results in a reduction of their inhibitory role both in central pain perception and presumably in the more anterior parts of the brain to which the axons project including the limbic system and the neocortex. Since the serotonergic and adrenergic systems are antagonistic this reduction in 5-HT turnover is consistent with the symptoms of an overactive hypothalamus and S.N.S. Any factor further increasing adrenergic functioning (e.g. any arousal factor such as anxiety) further accentuates the imbalance, and those reducing it (e.g. sympathetic nerve block, relaxation therapy) reduce it. Sub-

stances acting as serotonin-releasing factors (tyramine, phenylethylamine and free fatty acids have been implicated) would remove serotonin from its stores (serotonin is bound to neurons whose perikaria reside in the raphe nuclei and the hypothalamus and mid-brain contain relatively large amounts of serotonin) and such a loss would further derange functioning of such neurons, and presumably permit heightening of the hyperexcitability of neurons upon which they normally exert an inhibitory influence. At present the knowledge of the multiplicity of biochemical and neurogenic factors as well as the involvement of any positive and negative feedback loops is insufficient to give a completely integrated picture of the path from the MAO deficit to a full-blown attack. Of direct importance to this study is what is known of the possible mechanisms that could explain the involvement of bright light and flicker as precipitants and aggravating factors in migraine. While a number of authors cite, or give evidence for these as precipitants (see section 1.6) no specific mechanisms are postulated other than, as Sacks (1973) suggests, that they function as an arousing factor. Bruyn (1976) went so far as to write:

"..... the neurophysiopathological approach is open to further development; as yet we have no answers to such questions as why migraine can be elicited by exposure to strong light in some people."

Bruyn was overstating the case for, apart from the arousal suggestion, a specific mechanism was proposed by Herberg (1975). He suggested bright light might act by inhibiting the synthesis of pineal melatonin, a derivative of serotonin, which is able, among other things to raise the serotonin content of the mid-brain. Exposure to strong light, for even a minute or two, would thus cause a reduction of serotonin levels by inhibiting the synthesis of melatonin and so prevent any

increase in midbrain serotonin from this source. Herberg added the further suggestion that the customary preference for a darkened room during a migraine attack could be a physiological stratagem for stimulating pineal activity.

The implications of this for the present study are that, firstly one might expect the biochemical aspects and presumed hyperexcitability of the central structures to be reflected in the electrical activity of the brain. Secondly, that responses to photic stimulation should also reflect this hyperexcitability, and, in the light of the suggestion by Herberg (1975) mentioned above, even enhance it. Electroencephalographic and evoked potential techniques used to demonstrate this electrical activity are considered in the next chapter. A further aspect of relevance is another condition associated with neuronal hyperexcitability, that is epilepsy, but in particular to photo-sensitive epilepsy and this is considered in section 1.9.

## 1.8 Electroencephalography (EEG) and visual evoked potentials (VEP)

An extensive literature is already available on the development of electroencephalography and evoked potential recording, the techniques used and their clinical and research usage, and the reader is referred to these, particularly Kiloh, McComas and Osselton (1972); Regan (1972); Cooper, Osselton and Shaw (1974); Harding (1974); Remond (1976); Scott (1976) and Desmedt (1977). As the literature mentioned above is up to date I shall not seek to repeat much of it here except insofar as it bears on the development of this thesis and its conclusions, hence the purpose of this chapter is to extract and summarize from the literature

- (a) Definitions and descriptions of the types of electrophysiological data that were relevant to this study.
- (b) Factors affecting electrophysiological recordings of the types to be obtained in this study, and which need to be considered when planning the experimental design.
- (c) Data on the effects of substances implicated in the underlying mechanisms of migraine, with a view to prediction and interpretation of the results obtained

Techniques of analysis will be only briefly mentioned here and discussed more fully in section 2.7 on the analysis of the results obtained in this study.

The electroencephalogram (EEG) is a recording of electrical activity which originates in the bodies, dendrites and axons of cortical ganglion cells and in cells in subcortical grey matter. Impulses conducted to the cortex by way of the long ascending tracts especially



from afferent receptors and from thalamic relays contribute in various ways to the EEG. The EEG activity is also modified by excitatory and inhibitory synaptic processes in the cortex, by 'recruitment' of the participating elements and by processes of summation and integration which are not yet fully understood. Moreover impulses arising in the reticular formation in the brain stem also control basic cortical and thalamic activity.

The human EEG represents oscillations of electrical activity varying in frequency from about 1 to 40 cycles per second (c/sec.) and in amplitude from about 10 to 300  $\mu$ V. As a matter of convenience, the EEG frequency spectrum is divided into bands that are designated as follows:

- Delta: less than 4 c/sec.
- Theta: from 4 c/sec. to less than 8 c/sec.
- Alpha: from 8 c/sec. to 13 c/sec. inclusive
- Beta: more than 13 c/sec.

Modern recording equipment usually has between 8 and 16 recording channels which enables simultaneous tracings from symmetrical areas of both sides of the head. The equipment also provides the high amplification required to record the signals through the intact skull and scalp. To obtain the EEG electrodes are placed on symmetrical positions on the scalp. A widely accepted method for determining the sites of electrode placement is the 10-20 system devised by Jasper and clearly described by Harding (1974). Those placements used in this work or subsequently referred to are illustrated in Fig. 1.3.

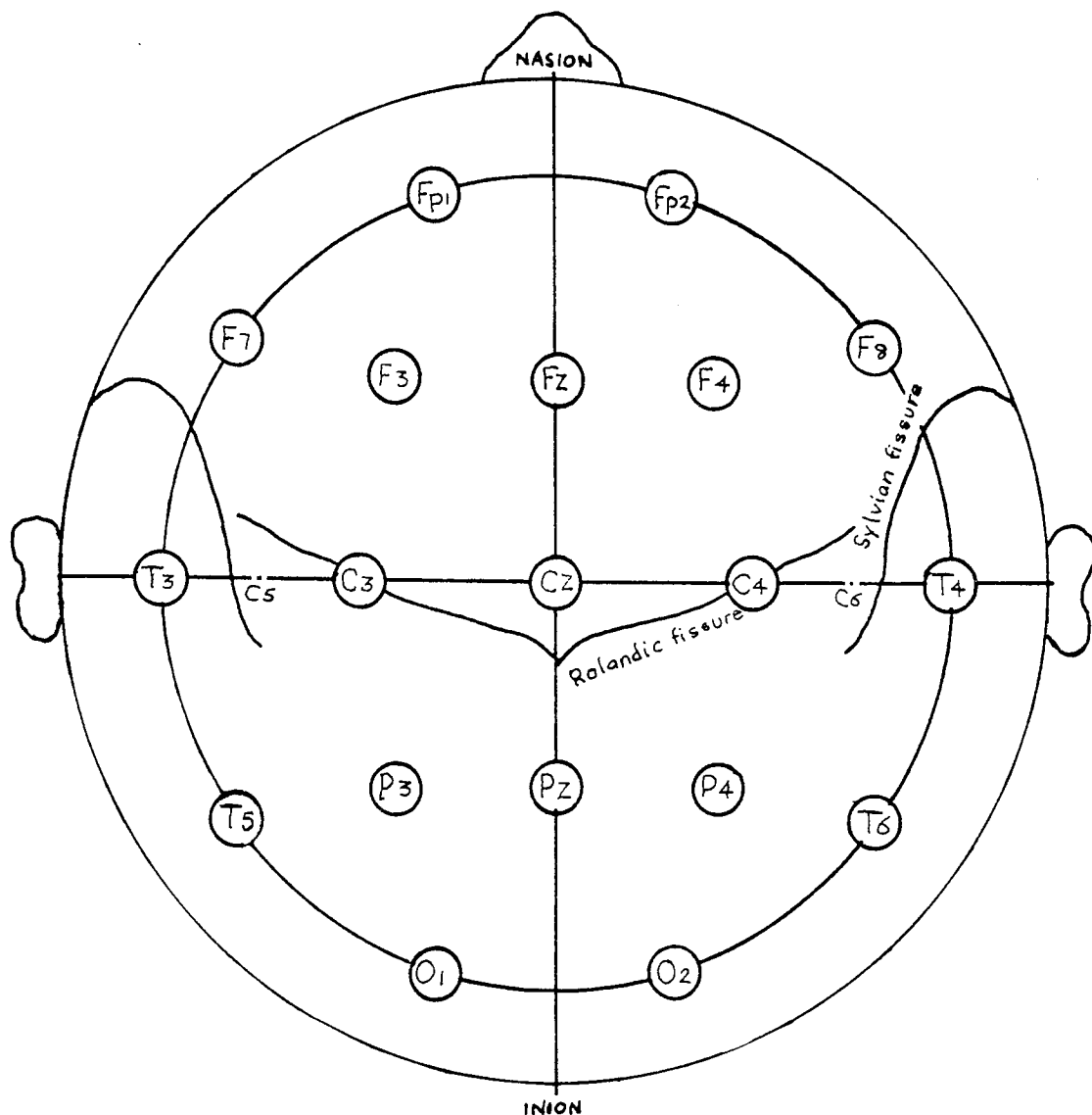


FIG. 1.3 Single plane projection of the skull showing electrode locations referred to in this study, with their designations. In addition the position of the main fissures are shown. The designations are as follows: frontal pole (Fp); frontal (F); mid-temporal (T3 and T4); posterior-temporal (T5 and T6); central (C); parietal (P) and occipital (O). (After Jasper, 1958).

Despite the complexity of the central nervous system, the vast number of active cells in the brain and the continuous variations in brain activity reproducible basic normal patterns can be identified in standard recordings. In infancy and childhood the normal EEG activity is slower than that found in adult subjects. The normal waking or resting record in adults is found in healthy subjects fully awake, adjusted to their physical environment and physically and mentally relaxed. This pattern changes in a predictable way during sleep or intense mental activity, but these changes will not be discussed in detail here. The adult resting record is well organized, especially in the parietal and occipital areas where 'alpha' activity is most prominent. This activity is seen most clearly when the subject's eyes are shut, and generally attenuates on eye opening. It appears symmetrically on both sides of the head but is usually a little lower over the dominant hemisphere. Beta activity is found to some extent in the EEGs of almost all normal adults and is usually low in amplitude. It can occur in a variety of locations in different subjects but is most often seen in the precentral regions. When it occurs posteriorly it may well be masked by the alpha rhythm and only be seen when the subject's eyes are open.

The EEG may change under a variety of conditions. Slowing of activity, usually associated with an increase in amplitude, is seen as the result of physiological or pathological lowering of brain cell metabolism. This may occur in deep sleep, in coma, and as a result of a decrease or impairment of the cerebral blood supply. Hyperventilation (over-breathing) is used as a standard provocative procedure as it has a vaso-constrictor effect on cerebral arterioles thus reducing cerebral blood flow and so causing ischemic anoxia. The characteristic hyper-

ventilation response is a fluctuating crescendo of bilaterally synchronous slow activity, initially of theta frequency but slowing usually to 3 c/s. The response may be posteriorly or anteriorly predominant and normally disappears within half a minute of the end of over-breathing. The response is clearly seen in normal children but much less marked in normal adults although there is wide individual variation. The amount of slow activity evoked is increased in all subjects by quite mild degrees of hypoglycaemia, such as may be present 3 hours after a meal. The hyperventilation response is abnormal if

- (a) it is prolonged after over-breathing has ceased and hypoglycaemia is absent
- (b) the response is consistently asymmetrical which indicates a lateralized or focal abnormality
- (c) epileptiform discharges are evoked (see section 1.9).

The focal appearance of slow wave activity is usually indicative of a disease process such as a neoplasm or other space occupying lesion, or else degenerative, vascular or inflammatory conditions. Transient slowing of EEG activity generally may be produced by alcohol or certain drugs (e.g. ergotamine, see section 1.10).

Faster than normal activity is seen when cerebral activity is increased from the basic state for physiological or pathological reasons. Such activity occurs in the appropriate cortical area following sensory stimulation and as a diffuse change during concentrated mental activity or during states of tension or anxiety. Some drugs, including barbiturates, dexedrin and antidepressant agents, may produce abnormally fast activity. Certain epileptiform discharges appear as high-voltage fast activity in the form of discrete spikes. These may be seen as

the result of irritative lesions or of pathological over-excitability of the cortex as seen in convulsive states. Another form of paroxysmal discharge is the spike-and-wave activity, which consists of an alternation of high voltage spikes or groups of spikes with high voltage slow wave activity. Paroxysmal discharges almost always start and stop abruptly. They may appear in a sharply localized area or involve all brain areas simultaneously. Paroxysmal discharges are discussed more fully in section 1.9.

In addition to factors mentioned above the EEG may also be affected by changes associated with sleep deprivation and fatigue (factors which should not affect this study), the age of the individual (subjects were age-matched to control for this, see section 2.2) and by both circadian rhythms and the menstrual cycle (changes due to these factors are well covered by Harding and Thompson, 1976). It was intended to balance the experimental design so that circadian rhythms would not bias the comparison between migraine patients and controls and therefore these are not discussed further.

The menstrual cycle and associated EEG changes are briefly considered by Bell, Christie and Venables (1975) and more fully by Harding and Thompson (1976). It is thought the changes in levels and proportions of oestrogen and progesterone may be either directly or indirectly responsible for the variations in the EEG observed during the course of the menstrual cycle. Harding and Thompson (1976) after reviewing the literature concluded the following pattern for the basic EEG emerges

- (a) in the preovulatory phase (day 5-14) the alpha frequency is higher, and the amount of beta activity is increased,
- (b) in the postovulation or luteal phase (day 15-25) the alpha is slowed and increased in amount, there is less beta and more theta activity,
- (c) in the premenstrual phase (day 25-28) alpha frequency is higher and reduced in amount, there is more beta activity, less theta activity and a general reduction in EEG energy,
- (d) in the menstrual phase (day 1-5) the alpha is slowed and increased in amount, there is less beta activity and more theta activity.

Thus, the stage of the menstrual cycle needs to be considered when assessing the EEG of a woman. Ideally studies should control for the stage of the menstrual cycle but this is rarely done. Often it is not feasible due to various constraints such as the availability of subjects and of laboratory facilities. The influence of the menstrual cycle on responses to intermittent photic stimulation (IPS) is discussed below.

The use and usefulness of photic stimulation in routine clinical electroencephalography is discussed by Hughes (1960); Jeavons (1969); Cooper, Osselton and Shaw (1974) and Scott (1976). Photic stimulation is a widely used evocative technique and can be a potent epileptogenic agent. Thus the first reason for its use is to ascertain whether abnormal epileptiform discharges are evoked and such photosensitive epilepsy as discussed in section 1.9.9. The second reason for using IPS is to examine the EEG for 'photic driving' or 'photic following'.

Photic driving is defined as a rhythmic response seen mainly in the occipital regions which appears in response to IPS at the same rate as the flash or as a harmonic or subharmonic of the flash rate. These responses are usually symmetrical and while the fundamental responses are sinusoidal the presence of higher order harmonics produces a waveform which Jeavons (1969) describes as often sharp with one half-cycle being pointed like mu rhythm. Hughes (1960) found that 33% of the 1,326 subjects he examined showed no evidence of photic driving on visual inspection. Jeavons (1969) reports that Butcher and Chase in a 1965 study found no visible response in 27% of subjects using low intensity light (a figure similar to that of Hughes) but that increasing the intensity of the light increased the number of cases in which the response could be seen. Hughes (1960) reported another factor as affecting photic driving, that is beta activity, for while 29% of all subjects showed good or excellent driving, 45% of those with prominent beta rhythms in the resting record showed good or excellent driving. Background activity often obscures photic driving when a visual inspection is made. Use of a low-frequency analyzer helps detect a photic driving response and will reveal harmonic and subharmonic components of the driving not always discernible by eye alone. Methods of frequency analysis were initially studied (Harding, 1971; Winzer and Shamir, 1973; Davis, 1973; Cooper, Osselton and Shaw, 1974; Fukushima, 1975; Walter, 1976) as it was hoped to use some form of automated analysis of photic driving. Regretably such a facility did not become available in time to be used for this study and therefore not only did the proposed experimental method have to be modified but also time-consuming methods of analyzing the photic-driving in the raw EEG had to be undertaken. These issues are discussed in section 2.6.

Photic driving is regarded as a normal response. It is usually seen symmetrically, although the response can be somewhat asymmetrical. Jeavons (1969) considers an asymmetry greater than 50% should be regarded as abnormal, with the side showing reduced photic driving being associated with cerebral pathology.

At slow rates of flash (below about 5 f/sec.), the response to IPS does not appear as photic driving but as a series discrete responses. These visual responses or visual evoked potentials (VEP) in the occipital cortex may not exceed 10 microvolts by the time they reach the scalp and often these signals cannot be detected reliably by visual inspection of the EEG within the much greater spontaneous activity of the brain at that point (Perry and Childers, 1969; Harding, 1974). Methods of detecting these signals in the background 'noise' of the spontaneous activity are described by Cooper, Osselton and Shaw (1974), Walter (1976) and Desmedt (1977). The widely used averaging technique makes the assumption that a repetitive stimulus produces a repetitive response. Therefore within a set time interval following the stimulus

- (a) the evoked response (signal) will occur at a similar time after that stimulus (i.e. it is time-locked) and will have a similar morphology, and
- (b) that the spontaneous brain activity (noise) will be random in relation to the stimulus.

Thus when a number of such time intervals are averaged the random 'noise' activity will average out thus revealing the average evoked activity; this is clearly illustrated by Harding (1974). The averaging process is usually carried out by a digital computer, and in practice, between twenty-five and several thousand responses have



been averaged to obtain a VEP but 25 to 100 are usually sufficient.

The generalised configuration of a VEP to slow flash rates as obtained and classified by Harding (1974) is given in Fig. 1.4a, and this is the classification used by the Neuropsychology Unit. An example of a VEP recorded to a slow flash rate is given in Fig. 1.4b. Other classifications have been developed for evoked response records and examples of these, with discussions on their relative merits, are given by Bergamini and Bergamasio (1967), Perry and Childers (1969) and Regan (1972).

The difficulties experienced in classifying the morphology of the VEP were in part due to its variability in relation to experimental conditions and subject variables. The experimental variables include flash duration and frequency of IPS, radiant energy or brightness of the flash, stimulus wavelength or colour, pattern stimulation, binocular and monocular stimulation, retinal location and stimulus size, and retinal adaption level. The subject variables affecting the VEP include age and sex, visual acuity and pupil size, dominance, habituation and electrode location. These factors are considered in detail by Bergamini and Bergamasio (1967); Perry and Childers (1969) and Regan (1972) and those points pertinent to this study are summarized from these texts below.

Perry and Childers give the most comprehensive coverage of the effects of flash duration and frequency of IPS in normals. The effect of flash duration upon the VEP has not been extensively studied. When, as in this study, a stroboscope is used the stimulus duration is brief and pulse-like, with the VEP considered predominantly an 'on'

FIG. 1.4a Generalized configuration of the visual evoked potential showing all known components. The nomenclature used is the system employed at the Neuropsychology Unit (see Harding, 1974). Positive components exhibit a downward deflection and negative components an upwards deflection.

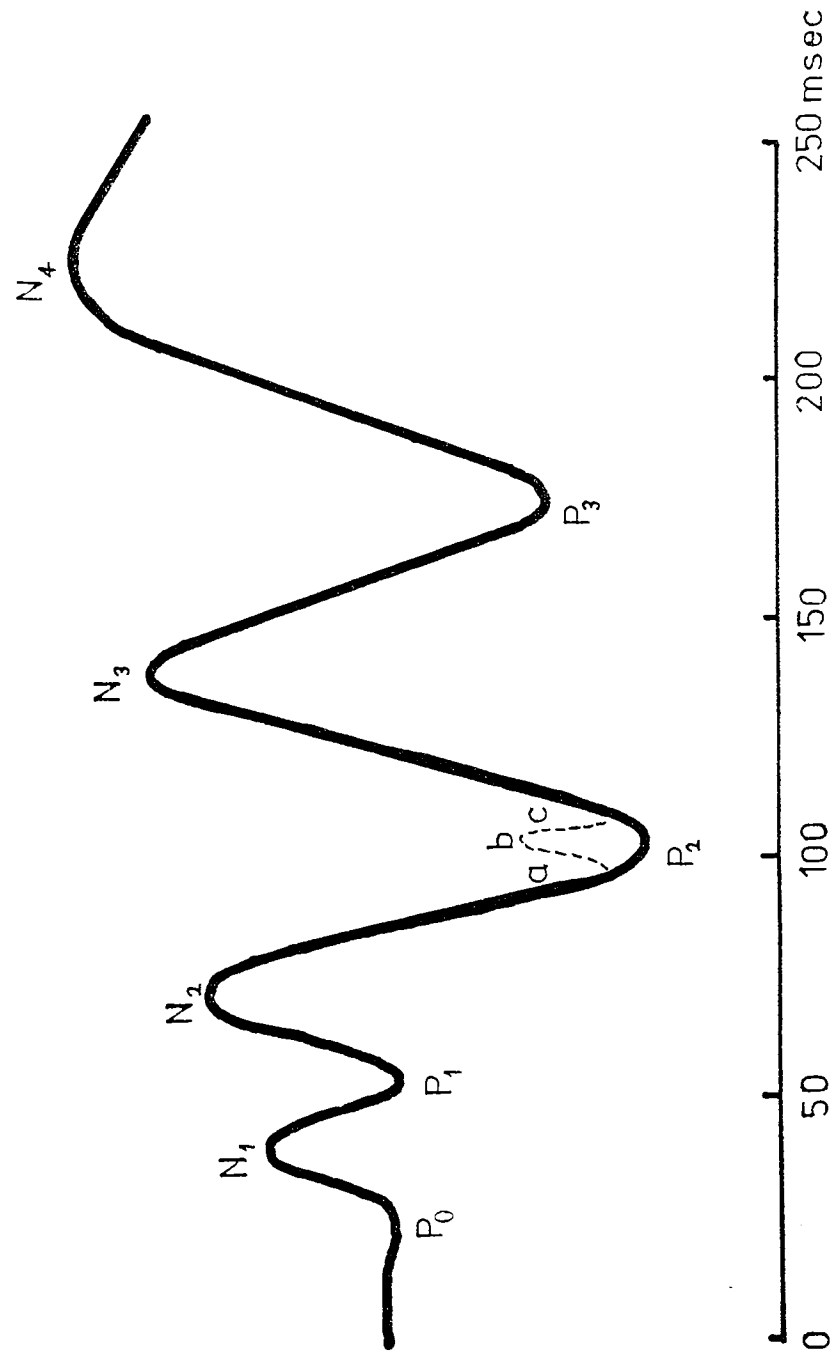
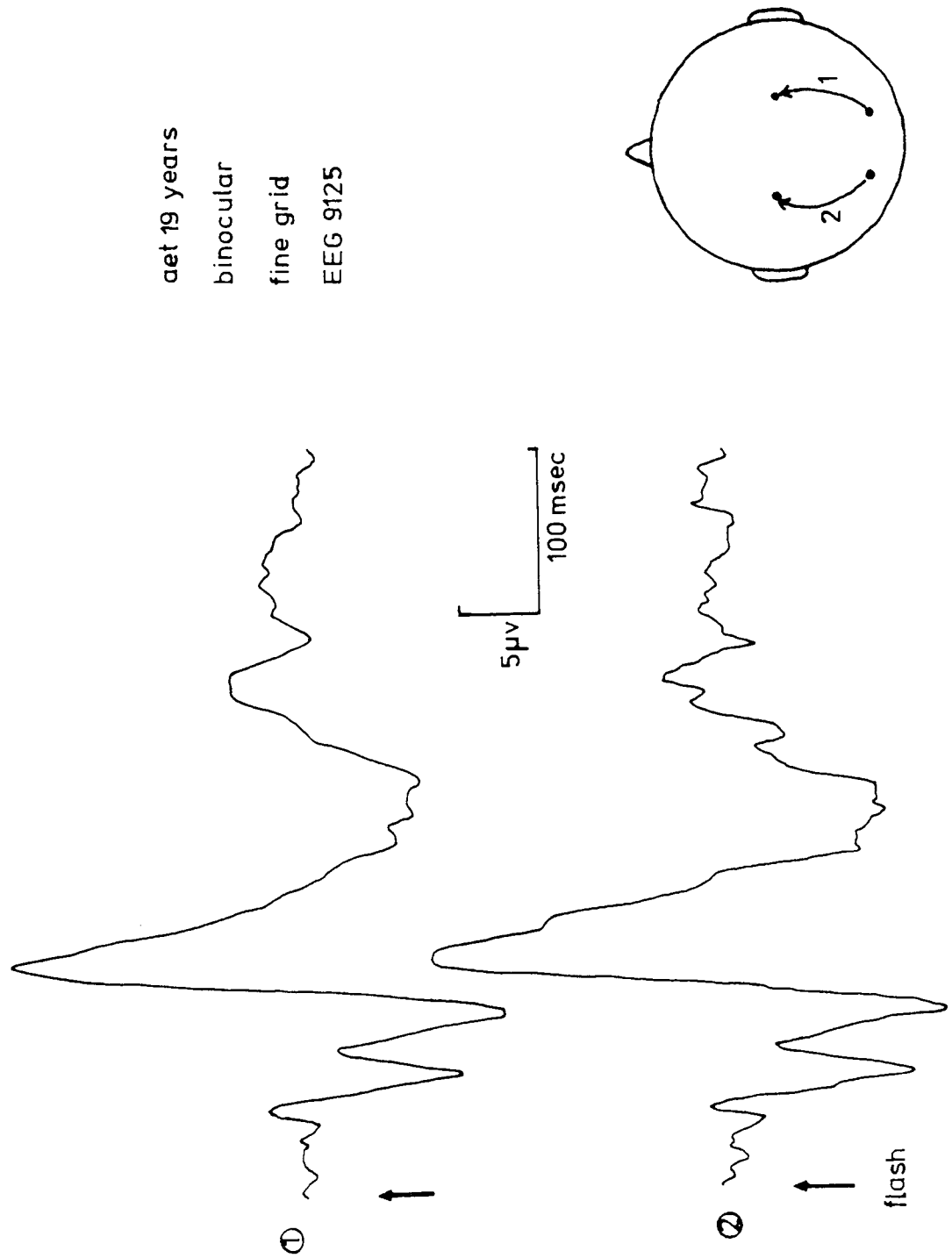


FIG. 1.4b

Example of a VEP obtained from a normal subject clearly showing the main components of the VEP (see Fig. 1.4a). The response being obtained to 25 flashes at 2 f/sec., with the stroboscope set at Intensity 2 and 30 cm. away from the subject's eyes, which were open.



response. Attempts to record a total VEP have commonly used flash rates of one per second or less, on the assumptions that the response requires a finite amount of time to be completed and that the interruption of the response by another flash produces a contaminated response and therefore it is only at these slower rates that the VEP remains intact. The determination of where a given VEP ends is more difficult than determining where it begins, even to IPS as slow as one flash every few seconds. Nevertheless Perry and Childers consider empirical evidence supports the above assumptions in that as the frequency of stimulation is increased beyond 3 flash a second (f/sec.) the response tails overlap the next response and add to it. An examination of Fig. 1.4c shows how the response to low flash rates resembles the configuration shown in Fig. 1.4a and 1.4b but as the flash rate increases it takes on the appearance of a fundamental photic driving response mixed with faster components. Perry and Childers note that an increase in the rate of stimulation of white light produces a rather constant response size up to approximately 8 f/sec., at which point the response size becomes larger reaching a maximum around 10 f/sec. and then decreases in size as the stimulus rate is further increased. This corresponds well to the findings of high amplitude photic driving around 10 f/sec. in normal subjects reported by Golla and Winter (1959) (see section 1.10) and is discussed further in section 3.

Radiant energy and brightness will be considered next. In general, increasing the intensity of stimulation produces VEPs which are characterized by greater complexity, greater amplitude, and shorter latencies. However, extremely intense stimulation can produce a reduction in VEP size. Intense stimulation is also reported as



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FIG. 1.4c

Figure reproduced from Perry and Childers (1969) showing the response of a normal subject to different rates of IPS.

reducing the amplitude of photic driving (Montagu, 1967).

The effect of stimulus wavelength or colour upon the VEP is unclear. Perry and Childers (1969) and Regan (1972) state it is difficult to summarize studies on this aspect because there have been wide variations in experimental procedures and little systematic or extensive work. However, they suggest different wavelengths may produce different VEP shapes. This study used only a stroboscope giving out white light. Slatter (1968) studied migraine patients and used a stroboscope emitting white light on some and a stroboscope emitting an orange-red light on others. He considered the orange-red light to be more effective in producing photic driving than the white light but since he gives only the intensity of the orange-red light it is unclear whether this enhancement is a wavelength effect or an intensity effect. The role of colour in PSE is considered in section 1.9.9.

Pattern stimulation is of particular relevance to this study as when IPS is used to test for PSE (see section 1.9.9) a fine grid or pattern of small squares in which the squares subtend a visual angle of approximately  $20'$  has been found the most potent for provoking the characteristic EEG abnormalities (Jeavons et al, 1972; Jeavons and Harding, 1975). In addition, the texts mentioned above, White (1975) and Ikeda (1976) report an increase in the amplitude of the  $P_2$  component in normals when an increasingly fine grid is presented at the same luminance. However, reducing the sharpness of the pattern, or defocussing it, produces VEP changes, including a reduction of the  $P_2$  component, whereas defocussing simple spots of light has little or no effect on the VEP. Thus some control or check on the visual acuity of subjects is to be preferred when using pattern stimulation (see section 2.6).

Generally, binocular responses are very similar to either monocular responses in subjects with normal vision. However, an occlusion of one eye the photoconvulsive threshold (see section 1.9.9), is found to increase quite considerably, associated with which is a decrease in the amplitude of the occipital spike of the VEP, (Jeavons and Harding, 1975), as compared with the binocular condition under the same stimulus conditions. Thus for this study it was considered necessary to check that subjects had not lost the use of one eye (see section 2.6).

The size of the stimulus and its retinal location can affect the VEP. Stimuli ranging in size from 0.06 degrees to essentially full-field have been used. Most reports agree that with relatively discrete stimulation there is a decrement in response size as the stimulus is moved peripherally away from the fovea. Also, if the stimulus size is increased over a given retinal area, there is a small but corresponding increase in VEP amplitude, with full-field stimulation the response is maximal. Thus it is important that when using a stroboscope to produce IPS it should be kept at a constant distance and the direction of gaze of the subjects should be controlled. Jeavons (1969) recommends the lamp should be placed 30 cm. from the subject's eyes. At this distance it is possible to see the subject's face and so observe any jerking (which may accompany epileptic discharge); see if the eyes are properly open or closed and finally see if the subject is looking straight at the lamp. He also recommends the lamp should be straight in front of the subject's eyes so they can look at the centre in comfort, that a diffusion screen be placed in front of the lamp and a small circle marked at the centre to act as a target for the subject to look at throughout IPS. These recommendations were followed in this study (see section 2.6). Jeavons (1969) notes that

at 30 cm. photic driving can be seen in most patients, so it was assumed this distance was satisfactory for this study, i.e. for examining photic driving responses in migraine. Previous research on photic driving and migraine is considered in section 1.10.

Both Jeavons (1969) and Perry and Childers (1969) recommend standardization of background illumination (by drawing blinds and using artificial light). Perry and Childers point out, firstly, that background illumination (a continuously on surround field) maintains the retina at a constant adaption level above which the IPS is seen. Secondly, that used alone, IPS produces fluctuations in the adaptation level which are difficult to measure, and finally, that it is highly likely that some of the variations in the individual responses within a VEP are related to changing states of adaptation. They conclude that to obtain experimental control of this variable it is probably adequate to ensure a common adaption level throughout the experiment. Jeavons (1969) commented that, on the one hand, the effect of photic stimulation is enhanced if the room is darkened, and on the other hand that there should be sufficient light to permit proper observation of the patient. Therefore this study was carried out in a room lit only by artificial light at a set level of low illumination (see section 2.6).

As Regan (1972) points out the subject variable of pupillary diameter could be expected to affect the intensity of light reaching the retina to some extent, however he considers the relationship between pupil size and VEP size to be unclear. In studies of migraine and VEP responses (see section 1.10), Lehtonen (1974) dilated his subjects' pupils with tropicamid drops and thus removed individual variation.



He found this dilation increased VEP size in both the migrainous and controls but gives no details of the relative increase. Richey et al (1966), on the other hand, did not dilate their subjects' pupils, but measured pupil size both pre-test and post-test and on both occasions found the migraine patients to have significantly smaller pupils ( $p < 0.001$ ). Whether this difference in pupil size would be sufficient to account for their finding of a significantly lower amplitude  $P_2$  in the migrainous remains a matter of speculation (see section 1.10). One aim of this study was to compare the VEPs obtained from the migrainous to those reported in the literature as characteristic of PSE (see section 1.9.9), and as these latter were obtained in patients with untreated pupils the subjects' pupils were not dilated in this study either.

Although Harmony et al (1973) found no significant interhemispheric differences in VEP amplitude, Perry and Childers (1969) consider it is likely that recording over the dominant hemisphere will give a larger amplitude VEP than those obtained from the non-dominant hemisphere. As the averages used for this study provided only two channels with good resolution, one of which would be needed for the strobe output, it was decided to record VEPs from the dominant hemisphere.

Two further factors which needed to be controlled were the subjects' age (Dustman and Beck, 1969) and sex (Bergamini and Bergamasio, 1967; Perry and Childers, 1969) as these are thought to affect the VEP. Migrainous and control subjects were therefore sex-matched and measures employed to age match them are described in section 2.2.

Finally, habituation or fatigue (Perry and Childers, 1969; Regan, 1972; Sutton and Tueting, 1975) may affect the VEP causing a

fluctuating decline in response size with repetitive stimulation. Habituation is a transitory phenomenon and the VEP will revert to its initial size if novelty is introduced into the experimental procedure or if the subject is allowed a brief pause or interruption of the procedure. This study therefore took care to allow brief pauses between each flash rate of IPS administered and took care to involve each subject's interest (see section 2.6). Moreover Jeavons (1969) recommends that from the point of view of standardization and control it is preferable to expose the patient (or subject) to one flash rate at a time, rather than use a varying rate over a wide range.

Finally, Jeavons (1969) recommends that to maintain standardization and control the patient, or subject, should be told exactly what to do and exactly what is going to happen, so that surprise plays no part in the reaction to IPS. He considers one cannot compare responses unless this is done and care was therefore taken to follow this recommendation in this study.

The waveform of the VEP is affected by electrode location and therefore the electrode locations used in this study for VEP recording were the same as those routinely used by Jeavons and Harding (1975) in their work on PSE so that adequate comparison of results could be made.

The final part of this chapter considers data on the effects of substances implicated in the underlying mechanisms of migraine (see section 1.7) on EEG and VEP records. The majority examine the effect of MAO (see below) but Dierick et al (1976) examined the effect of prostaglandin E2 (one of the substances released early in a migraine attack) and concluded it does not alter the EEG in a significant way and does not induce seizures.

Studies considering the effect of MAO have examined the response to IPS. Some have reported a possible relationship between platelet MAO activity and the proneness to augment or to reduce the amplitude of the VEP with the increasing stimulus intensity. Buchsbaum et al (1973) found patients with manic-depression, these having relatively low level of platelet MAO, had large amplitude VEPs and showed a relatively great rate of increase in the VEP amplitude with increasing stimulus intensity. In contrast, they found, depressed patients, these having relatively high levels of platelet MAO, had small amplitude VEPs and a low rate of amplitude increase in comparison. A later study on 57 unselected psychiatric patients (von Knorring, Oreland and Perris, 1977) did not confirm this relationship between MAO levels and increasing intensity of the stimulus, they suggest it might be a feature of the affective disorders, related to some other factor rather than MAO levels.

However, von Knorring et al (1977) did find a significant positive correlation between platelet MAO and VEP components in the 57 psychiatric patients as follows. The platelet MAO specific to beta-phenylethylamine (MAO B) was correlated to the latencies of  $N_2$ ,  $P_2$  and  $N_3$  and also to  $N_2$  amplitude. The platelet MAO specific to tryptamine correlated with the latency of  $N_3$ . It is difficult to evaluate these findings in the absence of a comparison control group, since no comparison with normal subjects of the findings on platelet MAO levels or of the VEP findings was made.

Vogel and his co-workers have produced a number of reports on plasma MAO activity and photic driving responses (Vogel et al, 1971; Klaiber et al, 1972; Stenn et al, 1972; Klaiber et al, 1974; Vogel et al,

1974). They reported that the gonadal steroid hormones, oestrogen and testosterone inhibit the EEG driving response to photic stimulation and suggested the mechanism by which these hormones achieve their inhibition of EEG photic driving was through their known ability to inhibit MAO activity. Vogel et al (1974) consider MAO inhibition should result in enhanced central adrenergic functioning and write "Substances known to enhance central adrenergic functioning (nor-adrenaline : amphetamine) block the EEG driving response to light ..... while substances which block central adrenergic functioning (e.g. phenothiazines) enhance various aspects of the EEG driving response."

In the study by Vogel et al (1974) ten normal male subjects were studied over 6 weeks for part of which they received a MAO inhibitor and low MAO activity was associated with a reduced EEG driving response. They felt this provided good support for their suggestion that oestrogen and testosterone may indeed have affected the EEG through their capacity to inhibit MAO activity. In section 1.7 the literature reviewed included two suggestions of relevance here. Firstly that in the migrainous there is always a lower level of MAO activity than in normals but that this only becomes significant at the time of an attack. Secondly, that menstrual migraine is associated with the fall in progesterone levels and thus the relative increase in oestrogens which results in decreased MAO activity, which may in turn help produce a migraine. Thus one might expect to find in the migrainous the reduced EEG photic driving associated with low MAO activity. Unfortunately no direct comparison can be made between the work of Vogel and the work on migraine for the following reasons:

- (a) For the earlier studies (Vogel et al, 1971; Klaiber et al, 1972) the EEG driving response was defined as

"the evocation of alpha waves for two consecutive seconds, or evocation of the EEG waves at the fundamental or harmonic frequency of the photic stimulation for two consecutive seconds, with no

other EEG waveform being visually detectable during that time." (Klaiber et al, 1972).

This definition is at variance to that generally used in studies of photic driving, for the evocation of alpha waves is not considered to constitute a photic driving response. However the study by Vogel et al (1974) uses a more conventional definition of photic driving that is:

".... the evocation of EEG waves at the fundamental or harmonic frequency of the photic stimulation for one full second, with no other EEG wave being visually detectable during the time."

- (b) They used stimulation trials lasting 10 seconds, therefore, relatively brief responses as well as those lasting for most of the 10 seconds would be both positively scored. Studies on photic driving in migraine (see section 1.10) have been mainly concerned with the prominence of photic driving at different IPS rates rather than straight presence or absence.
- (c) When Vogel and his co-workers state there is a change in EEG driving response they are referring to an overall response. That is the average number of positive scores (see above) to a number of flash rates (5, 10, 15, 20, 25 and 30 f/sec.) at each of 3 intensities (2, 4, and 8 of the Grass intensity scale), i.e. there is a maximum score of 18. Thus one cannot determine to which rates and to which intensities these positive scores were obtained, or the relative importance of these two variables in accounting for the reported variation in the photic driving response. Thus this work cannot be directly

compared to that on migrainous subjects where responses to individual flash rates are reported.

In conclusion, previous studies on levels of platelet MAO and the response to IPS are not helpful for predicting or interpreting any results found in migraine.

1.9 Migraine and the possibility of a relationship with epilepsy,  
with a description of aspects of photosensitive epilepsy

Photosensitive epilepsy (PSE) is provoked by certain types of visual stimulation, notably flickering light, and at the University of Aston in Birmingham, Professor G. F. A. Harding in collaboration with Dr. P. M. Jeavons has carried out research into this condition for over fifteen years (Jeavons and Harding, 1975). Dr. K. M. Hay, at the nearby Migraine Clinic, had noted that a number of his patients reported flicker as a precipitant of their migraine attacks (Hay, 1975). A possibility therefore arose that a similarity of these two sub-groups might exist, particularly in view of the suggestions made over the years of a possible relationship between migraine and epilepsy. Since no previous work specifically comparing these two sub-groups is known, this chapter will review the literature considering a relationship between migraine and epilepsy and conclude with an examination of certain aspects of PSE with a view to answering the following questions:

- (a) how strong is the evidence for a genetic relationship between migraine and epilepsy?
- (b) are the types of visual stimuli which precipitate migraine or PSE the same or do they differ for the two groups?
- (c) does PSE exhibit specific electroencephalographic or evoked potential characteristics, so it will be possible to check the EEGs and VEPs of the study group with flicker-induced migraine for such characteristics?

### 1.9.1 Definition and classification of epilepsy

Epilepsy can be defined as a tendency to recurring seizures (Kiloh, McComas and Osselton, 1972; Huott, Madison and Niedermeier, 1974; Scott, 1976) but Scott prefers the wider definition of 'Epilepsy is a sudden and usually repeated behavioural change associated with impairment of consciousness lasting seconds or minutes accompanied by abnormal electrical discharge in the brain.' The epileptic phenomena result from instability of all membranes of particular neurons, leading to sudden rapid and excessive neuronal discharges which are prolonged and spread rapidly (Fields and Raskin, 1976; Scott, 1976). Scott (1976) separates the abnormal brain activity associated with epilepsy and seen in scalp recordings into three types.

- (a) spikes, (regarded as the basic phenomena), which relate to the excitatory phase and appear in a generalised fashion during convulsions.
- (b) slow wave activity or 'flattening' is seen after a convulsion and relates to the inhibitory phase.
- (c) a combination of spike and slow wave, characteristic of petit mal epilepsy, is seen where the slow wave immediately follows the spike and Scott reports that this can be viewed as a condition in which inhibition builds up appropriately, preventing a minor attack becoming a major one.

Gloor (1975) considers the definition and distinction of spikes and sharp waves in detail.



Epilepsy has been classified in various ways involving clinical symptoms and electroencephalographic features but regardless of these a fundamental division is made between symptomatic and idiopathic epilepsy (Kiloh, McComas and Osselton, 1972; Scott, 1976; Tsuboi and Christian, 1976). The term symptomatic epilepsy implies epilepsy arising as a secondary brain dysfunction, that is, as a symptom of damage to the brain or as a symptom of a disease state; for example, epilepsy may be associated with brain tumors, head injury, phenylketonuria, heart disease, renal failure or tetanus and episodes of fever in infancy (febrile convulsions). Conversely idiopathic epilepsy refers to cases where such causes are unknown and the influence of possible genetic factors are inferred. This is an important distinction when considering a possible relationship between migraine and epilepsy, for where the two conditions occur in one individual this could be due to any of the following possibilities (Slatter, 1968).

- (a) idiopathic migraine and idiopathic epilepsy, where both are genetically independent and occur together by chance alone
- (b) idiopathic migraine and idiopathic epilepsy, where they are genetically related
- (c) idiopathic migraine and symptomatic epilepsy, where the epilepsy is the symptom of an acquired lesion (Parsonage, 1975; Cabral and Scott, 1976). Permanent brain damage can be caused by severe migraine (see section 1.4.6) and an example of a case where this is thought to have caused symptomatic epilepsy is given by Barolin (1966).

- (d) idiopathic migraine and symptomatic epilepsy where the seizure occurs at the height of a migraine attack and could be a symptom of the temporary biochemical changes, ischemia or edema that are associated with migraine (Carroll, 1968; Parsonage, 1975).
- (e) symptomatic migraine and idiopathic epilepsy. A combination for which no supportive evidence was found in the literature studied.
- (f) symptomatic migraine and symptomatic epilepsy. A possibility with certain conditions such as brain tumor, which may produce headaches with migrainous features (see section 1.2 and Appendix 1) as well as epilepsy.

In this connection, the ability to distinguish between idiopathic and symptomatic epilepsy would be welcome. According to Scott (1976) there are certain differences as follows. Symptomatic epilepsy may be regarded as exhibiting features of focal or partial discharge, although they may become generalized; are usually preceded by an aura; there is possibly a history of CNS insult and there is generally no family history of fits. (The focal epilepsy referred to would involve a cortical focus and may be restricted to a particular area, whereas generalised or centrencephalic seizures involve sub-cortical structures from which abnormal activity is projected to all cortical areas). In contrast, idiopathic epilepsy implies a seizure without aura; lack of evidence for a CNS lesion; a possible genetic factor in that a family history of fits may be found; and the EEG features of a generalised discharge as in grand mal and petit mal. These distinctions will be borne in mind when examining the evidence.

Various classifications of the types of epileptic seizure are given (Draper, 1974; Kiloh, McComas and Osselton, 1972; Scott, 1976) and as Jeavons and Harding (1975) point out this creates difficulty in assessing the incidence of various types of epilepsy because of the variations in classification. Fortunately, texts suggesting a relationship between migraine and epilepsy refer to epilepsy in general, thus interest lies in the overall incidence and in the demonstration of any type of epileptogenic activity in the migrainous. Therefore the various types of epilepsy will not be considered further, with the exception of photosensitive epilepsy.

#### 1.9.2 The factors involved in consideration of the literature on a relationship between migraine and epilepsy

A number of authors (Millichap, Lombroso and Lennox, 1955; Lennox and Lennox, 1960; Carroll, 1968; Hachinski, Porchawaka and Steele, 1973) refer to the works published by Liveing in 1873 and Gowers in 1895 and 1907 suggesting a close relationship between migraine and epilepsy, (see section 1.1.3), and many authors have given examples of migraine and epilepsy occurring in the same individual (Millichap, Lombroso and Lennox, 1955; Alvarez, 1959; Selby and Lance, 1960; Lennox and Lennox, 1960; Barolin, 1966; Ziegler and Wong, 1967; Carroll, 1968; Graham, 1969; Hachinski, Porchawaka and Steele, 1973; Poch, 1974; Pearce, 1976; Scott, 1976). However, the question is not can migraine and epilepsy occur in the same individual, but, do they occur together more frequently than one would expect by chance? If so, can the discrepancy be accounted for by cases of symptomatic epilepsy or is a common hereditary factor more likely? The additional questions concerning the possibility of a sibling relationship or other links in the family history are more complex to consider and will only

be touched on lightly in this study.

There are a number of questions that should be asked about reports of a relationship between migraine and epilepsy, for example

1. Are both the diagnosis of epilepsy and the diagnosis of migraine acceptable in terms of current thinking?
  - (a) do the clinical symptoms of the separate or combined attacks satisfy diagnostic criteria?
  - (b) does the similarity of some symptoms in the two conditions indicate a dual diagnosis could be inappropriate?
  - (c) if the publication bases its criteria for a diagnosis of epilepsy on the electroencephalographic findings, are these criteria currently considered inappropriate?
2. If the conclusions are based upon estimates of the incidence of the two conditions in the population, are these estimates inaccurate to a degree which would bias those conclusions?
3. Is sufficient account taken of the possible bias in the sample studied?
4. Is the conclusion that a favourable response to some anti-convulsants by some migrainous individuals indicates a relationship to epilepsy justified?
5. Do electroencephalographic findings, using currently accepted criteria, support the possibility of a relationship?

How pertinent these points are to studies considering a relationship between migraine and epilepsy will now be shown.

### 1.9.5 Diagnostic criteria in migraine and epilepsy

The problems of diagnosing migraine and the difficulties of establishing diagnostic criteria were considered in sections 1.2 and 1.3. The proportion of patients wrongly diagnosed as migrainous can only be guessed at, but it seems more likely that individuals with mild or atypical migraine will be excluded from diagnosis rather than non-migrainous individuals included. In contrast Jeavons (1975) and Jeavons and Harding (1975) report that 20% of patients referred to epilepsy clinics as having epilepsy and 20% of patients said to have epilepsy studied in a survey of psychiatric hospitals were found not to be suffering from epilepsy. Jeavons (1975) pointed out that temporary loss of consciousness, considered "the root symptom" of epilepsy by Lennox and Lennox (1960), may also occur in faints and syncope unconnected with epileptic seizures. Since temporary loss of consciousness may also occur in "basilar artery migraine", which is attributable to ischemia of the brain stem following vaso constriction of the basilar artery (see section 1.4), this may have resulted in some wrongly applied labels of 'epileptic' if the diagnosis was based on this symptom alone, a point made by Barolin (1966). Confusion can also be caused if there is extensive vascular dysfunction in the temporal lobe producing impairment of consciousness, a symptom leading to diagnostic confusion with psychomotor epilepsy (Barolin, 1966; Hall, 1971).

Generally the reader is unable to judge whether the criteria used by an author are appropriate, since the diagnostic criteria are not listed, and if the case histories are not given they cannot be inferred and one is left to rely on the author's clinical judgement. Two examples are given below where the criteria are given and can be

considered inadequate. Firstly Barolin (1966) in an otherwise good paper, considers "A headache of high intensity having a sudden onset and end" to be sufficient to diagnose migraine and does not consider it essential that one or more of the features of unilaterality, nausea or aura should be present. It is therefore likely that some of the patients he labels migrainous come outside the generally accepted criteria (see sections 1.2 and 1.3).

The second example illustrates how confusion can be added to the area, by again having a definition that may be too inclusive. Chao, Sexton and Davis (1964) consider cyclical vomiting in children as a form of autonomic epilepsy, although they clearly state that the characteristic features are 'the paroxysmal, periodic attacks of headache and a wide variety of autonomic dysfunction' (they list these features) and that 'other writers may elect to label such cases atypical migraine'. Their argument is not helped by their definition of a 'convulsive equivalent' as "an entity of epilepsy characterised by paroxysmal attacks of autonomic disturbances with or without associated seizures of other types, with or without disorders of other cerebral functions and with or without the 14 and 6 dysrhythmia." The reference to 14 and 6 dysrhythmia may be disregarded, as shown below, and the remainder of the definition is such that many of those it would cover, e.g. cases of classical migraine, would fall outside the definitions of epilepsy given at the beginning of this chapter. This lack of precision can only result in confusion.

Confusion also arises because many of the symptoms associated with the two conditions are described using the same nomenclature, but while this serves to indicate some commonality in the symptoms and

experience of the patients, it by no means ensures the origins are the same and it is these origins which are important to us, because they may well be different. It is therefore desirable to look at the symptoms, to see whether differences exist within what the nomenclature suggests are the same symptoms, for patterns suggesting differences in origin; patterns which are within themselves consistent.

One symptom that Poch (1974) felt could give rise to confusion is that of headache, since headaches may infrequently occur immediately after generalised epileptic seizure. However, no adequate study seems to have been done on the nature of the headache, i.e. does it show characteristics of a vascular headache, or of some other type?

Another area of confusion is that of abdominal migraine (see section 1.1.2) which is fairly well accepted as a migraine variant in which an 'aura' headache may or may not precede abdominal cramps, nausea and vomiting in some cases (Hall, 1971; Lundberg, 1975). However, it is also accepted that some epileptics will experience nausea, abdominal pain or other abdominal sensations as an epileptic aura (Livingston, 1951; Van Buren, 1963; Falconer and Taylor, 1970). It is unclear whether these abdominal sensations can be clearly differentiated except by an EEG at the time of attack.

It is the aura of attacks which, apart from the disorders of consciousness discussed previously, seem to present most scope for confusion (Barolin, 1966). Examples of epileptic aura (Lennox and Lennox, 1960; Falconer and Taylor, 1970; Ludwig and Marsan, 1975; Whitty, 1978), include paresthesia, aphasia, disorders of perception (including micropsia and macropsia), tinnitus and vertigo, and visual

disturbances. The visual disturbances (Ludwig and Marsan, 1975) include elementary sensations of light and colour in simple or gross form; flashing light and various patterns including zigzag lines of light, spots or stars, which may be reported as moving. As listed these aura are remarkably similar to some of those given for classical migraine (see section 1.4.2). However, while a simple listing would superficially indicate a close connection, it fails to disclose important differences, both in the nature of certain symptoms and in the underlying mechanisms thought to produce the brain dysfunction responsible for the aura. As previously noted no adequate comparison appears to have been made of abdominal sensations in the two conditions. Abnormalities of mood, behaviour and consciousness are suggested by Falconer and Taylor (1970) as being more likely to be epileptic when they are sudden, out of character, brief and irregularly recurrent. In sections 1.4.1 and 1.4.2 it was indicated that such changes may be out of character and irregularly recurrent in migraine sufferers, but they seem to be gradual in onset and their time span is seldom brief. These differences are more clearly seen in the disorders of sensation and perception. Such epileptic aura are reported as lasting a matter of seconds. Lennox and Lennox (1960) suggest a range of 10 to 20 seconds for epileptic aura, as opposed to 10 to 20 minutes being typical for migraine aura, although the figures that emerged from the review of the literature (section 1.4.2) suggested such aura often last 20 to 40 minutes in migraine. In addition, as described by Barolin (1966) and Graham (1969) the "march" of the epileptic aura is rapid whereas the spread of the migraine scotoma, hyperesthesia or aphasia is gradual. It appears that early writers had no alternative explanations for the migrainous aura other than that of some form of epileptic discharge. This explanation was



not unreasonable, for the spread of epileptic discharge (Kiloh, McComas and Osselton, 1972) may occur rapidly by conduction along neuronal pathways (trans-synaptic conduction) or more slowly by direct spread to contiguous neurons (ephaptic conduction). The latter is suggested to occur as a result of a failure of the inhibitory mechanisms (Brazier, 1974) so that neighbouring neurons respond to the electrical field set up by the initial neuronal discharge and it is this ephaptic conduction which results in the march of Jacksonian epilepsy. There is one major difficulty in employing such an explanation for migraine phenomena, for while the initial epileptic discharge may spread it also tends to be self-perpetuating itself; whereas the spreading wave of excitation in migraine is immediately followed by inhibition of activity and thus the neurons initially involved do not show perpetuation of excitatory activity. This characteristic of migraine aura is most clearly illustrated in reports on the classical migraine fortification spectra (see section 1.4.2) as described by such authors as Lashley (1941) and Richards (1971). Lashley (1941) is credited with suggesting these spectra were caused by a brief phase of intense neuronal excitation preceeding a spreading wave of cortical depression. The phenomenon of spreading cortical depression has been studied by Leao (1944) and Grafstein (1956), and recently Richards' (1971) observations support Lashley's view. At the present stage of research (Hachinski, Porchawaka and Steele, 1973) it seems that the vehicle for the manifestation of migraine aura is biochemical resulting in the neuronal excitation and in changes in vasomotor tone, in some cases vasoconstriction may be sufficient to produce ischemia, and possibly edema, which will prolong the depression of cortical activity. While the biochemical factor would appear to be dominant in the cortex it is conceivable that it originates outside

the cortex as biochemical changes in the raphe neurons, which are known to have connections with the cortex (Koella, 1977) and the hypothalamus and be susceptible to changes in their 5-HT levels (see section 1.7). There is a great paucity of literature comparing the neuronal biochemistry of migraine and epilepsy and such a comparison might resolve the question of any common origin for migraine and epilepsy.

The final query about diagnosis concerned papers where the diagnosis of epilepsy was based on EEG characteristics, and whether the criteria employed are currently considered inappropriate. Where such diagnosis has been assisted by the presence of spikes or spikes and waves in the EEG, as mentioned at the beginning of this chapter, such a diagnosis would not be refuted. There are however studies, principally those involved in the debate on whether cyclic vomiting in childhood can be diagnosed abdominal migraine, or should be diagnosed abdominal epilepsy, which use 14 and 6 cycle per second bursts as support for a diagnosis of epilepsy. Gibbs and Gibbs (1951) were the first to describe runs of 14 and 6 per second positive spikes in sleep EEGs and claimed that there was an association between this activity and attacks of "thalamic or hypothalamic epilepsy" in the waking state, which would normally go unrecognized as epilepsy. Kiloh, McComas and Osselton (1972) suggest that many of the patients described by Gibbs and Gibbs would usually be diagnosed as having atypical migraine. Descriptions of this activity may be found in studies considering cyclic vomiting in childhood as a form of epilepsy and Kellaway, Crawley and Kagawa (1960) put forward an eloquent plea in support of the Gibbs and Gibbs hypothesis. However other authors investigating cyclic vomiting or migraine in childhood either doubted whether 14 and 6 per

second positive spikes were seizure discharges (Millichap, Lombroso and Lennox, 1955; Whitehouse, Pappas, Escala and Livingston, 1967) or while suggesting they were controversial used them as supportive evidence for cyclic vomiting as form of epilepsy (Chao, Sexton and Davis, 1964). Kiloh, McComas and Osselton, (1972) review the 'confusing' and 'contradictory' literature and conclude that the significance of 14 and 6 per second positive spikes is to indicate immaturity and suggest it bears some resemblance to sleep spindles. They include a suggestion that the waveform is a product of harmonies, i.e. 14 and 7 (not 6) cycles per second and that the term 'burst' should therefore be substituted for 'positive spikes'. In the light of this, the studies on cyclic vomiting suggesting such activity as helpful in diagnosing epilepsy can be regarded as highly suspect.

Additional difficulty arises when authors, such as Livingston (1951), finding some of their subjects had ostensibly normal EEGs, suggested this could be because they had been unable to record the seizure discharges, rather than suggesting the individual was not epileptic.

It is known that epileptic attacks may occur without evident changes in scalp recording (Kiloh, McComas and Osselton, 1972; Gloor, 1975) and this may be due to any of the following:

- (a) the focal discharge is so discrete and of such low amplitude that it is not conducted to the surface
- (b) the discharge remains limited to subcortical structures
- (c) there is no hypersynchronization and so the EEG would tend to be of low voltage.

Since studies attempting to establish cyclic vomiting as a form of epilepsy have proposed it as an expression of thalamic and hypothalamic epilepsy, the second alternative would provide, in their view, a

reasonable explanation for any ostensibly normal EEG. However, such an explanation is a possibility and not a sufficient explanation for the absence of epileptogenic activity in cases otherwise diagnosable as having abdominal migraine or other types of migraine.

#### 1.9.4 Inaccuracy of estimates of population incidence

Conflicting conclusions have been reached as to whether migraine and epilepsy occur together more often than one would expect in the population. On the one hand authors such as Huott, Madison and Niedermeyer (1974) will write that in migraine patients epileptic seizures almost never occur, or make statements like that of Dalsgaard-Nielson (1974)

"Nor do our investigations concerning prevalence, intercoincidence, and provoking factors support a theory of a genetic relation."

Yet on the other hand some authors have concluded that there is an association between the two conditions, on the basis that given a person has one condition they are more likely to have the other than would be expected from population incidence figures for that other condition. It is therefore important to check the accuracy of the estimates of the population incidence that they used.

Examining first those studies looking at the incidence of migraine in epileptics, Lennox and Lennox (1960) found that 9.6% of parents of epileptics had migraine and concluded "in the parents of epileptics migraine is found perhaps twice as frequently as in the general adult population." Since they also found that in 1,610 epileptics 11.1% (9.3% of men and 13.4% of women) gave a personal history of migraine, and this confirmed in their view that epileptics had a much higher level of migraine than one would expect. A view shared by Ziegler and

Wong (1967) who quoted the above figures. Unfortunately the figure of about 5 per cent for the population incidence of migraine while widely accepted at one time is (as was seen in section 1.5) a gross underestimate. Taking the figures given by Waters (1974b,1975e) as a realistic estimate then migraine affects 15 to 20 per cent of men and 24 to 29 per cent of women, which yields an overall figure of about 22 per cent. Thus the figures Lennox and Lennox found are well within what one would expect by chance, as are those of Poch (1974) who found 14 of the 100 epileptics he studied also had migraine, and made no particular comment. Even before population based estimates of migraine were available, Alvarez (1959) was cautious about inferring any relationship between migraine and epilepsy when he found 21 per cent of the relatives of epileptics had migraine since he found 23 per cent of the relatives of 574 psychotic and alcoholic patients had had migraine and no-one had suggested migraine, as related to psychosis. Alvarez suspected that patients with mild or uncomplicated migraine do not consult a doctor for their complaint whereas those with migraine plus psychosis or epilepsy will complain about it when they visit the physician, a suspicion in part confirmed by Waters and O'Connor (1970) who found only 54 per cent of the women diagnosed as migrainous in a population study had ever consulted a doctor about their headaches.

Unfortunately, this non-consultation of physicians makes those studies of the incidence of epilepsy in the migrainous suspect from the start, whereas one might assume that most if not all epileptics consult a doctor and therefore the comparisons above are reasonably valid. One might also expect all those with both migraine and epilepsy to consult a doctor and therefore be over-represented in any group of migrainous

patients, whether such over-representation would be increased in those referred to specialist clinics is a matter of conjecture. The incidence of epilepsy in the population is reported as being around 0.5 per cent (Jeavons and Harding, 1975), although Lennox (1951) who reported that 0.5 per cent of American draftees were excluded because of epilepsy, felt this was underestimated as among other reasons, many men failed to report seizures that might be quiescent. Falconer and Taylor (1970) report that the College of General Practitioners estimate 0.4 per cent of the population to be epileptic; that the Isle of Wight Survey found 0.72 per cent of children aged five to fifteen to be epileptic and the figure from a general practice study by Pond was 0.62 per cent. Fogelman (1976) reported 0.6 per cent of 16 year olds as experiencing a fit in the previous 12 months. If one accepts 0.5 to 0.6 per cent as a reasonable estimate then the incidence of epilepsy reported in migraine patients is in excess of this. For example, Pearce (1976) reported that 2 per cent of patients attending a Migraine Clinic had epilepsy. The figure reported by Lennox and Lennox (1960) for 415 persons referred for migraine was 6.5 per cent. One cannot determine to what extent this excess is caused by over-representation of those with migraine and epilepsy in the patient group as opposed to the migraine population as a whole, and to what extent symptomatic epilepsy contributes to the excess.

Some authors have given figures for the percentage of patients with a family history of epilepsy, e.g. Selby and Lance reported 15 per cent of 439 patients as having a family history of epilepsy. A figure they consider in excess of normal. This might look a useful measure but since migraine patients, as discussed above, are likely to contain more epileptics than the migraine population as a whole and

since those with idiopathic epilepsy are likely to have epileptic relatives, as discussed earlier, this introduces one source of bias. Another source of bias arises as follows. If one accepts that migraine has some hereditary factor, although studies are not conclusive (Bille, 1962; Refsum, 1969; Ziegler, Hassanein, Harris and Stewart, 1975; Ziegler, 1977), then migraine patients will have more migrainous relatives than on average. If one also accepts that migraine can produce symptomatic epilepsy (although rarely), then the migrainous patients should have a greater percentage of relatives with such symptomatic epilepsy than controls. Both these sources of bias would confuse the issue of genetic relationship between idiopathic migraine and idiopathic epilepsy.

Thus while the percentage of epileptics with migraine is within what one would expect by chance, i.e. no apparent relationship between epilepsy and migraine, the figures for the percentage of migraine patients with epilepsy are in excess of expectation but sources of bias make it impossible to determine what the true excess, if any, is and so whether symptomatic epilepsy would account for the discrepancy.

#### 1.9.5 Possible bias in the samples studied

As indicated above, any group of migraine patients is likely to be unrepresentative of all migraine sufferers as regards the incidence of epilepsy if the following assumptions hold true.

- (a) more of the people suffering both migraine and epilepsy, than those suffering migraine alone, can be expected to seek help from a doctor

- (b) Of those suffering migraine accompanied by loss of consciousness or mental confusion, the majority consult a doctor and these conditions may be confused with epilepsy (see section 1.9.5).
- (c) People suffering any form of complicated migraine, especially if any persisting or permanent sequelae are marked, will consult their doctor and it is this group with severe migraine who are most risk of anoxia causing limited areas of brain damage. Such brain damage could be responsible for producing an epileptic focus, and thus symptomatic epilepsy, in a proportion of such cases. Barolin (1966) noted that the more atypical a migrainous case (accompanying symptoms, psychical irritation, long duration of attacks, etc.) the more probable an abnormal EEG.

In addition to the above possibilities only a proportion of patients are referred to specialists and these may be even more unrepresentative of the migraine population as a whole, than are those attending general practitioners (Barolin, 1966; Hockaday and Whitty, 1969).

On top of this patients receiving EEG investigation are obviously yet further selected in most studies. For example, Hockaday and Whitty (1969) when reporting on the EEG in 560 patients found a personal or family history of epilepsy, or both, was given by 126 patients (family 33, personal 82, both 11). However, they were careful to state that this high figure was partly determined by case selection, as there was a tendency to investigate more fully patients with a family or



personal history of epilepsy. Moreover, they concluded

"Because of this tendency, we consider it is not justifiable to use the material in this study for an evaluation of the possible link between migraine and epilepsy in the population at large."

Yet Huott, Madison and Niedermeyer (1974) while concluding linkage between migraine and epilepsy is a rare event, cite Hockaday and Whitty as supporting evidence for their statement that one of the bases for the assumption of a close relationship between migraine and epilepsy is observations of a higher prevalence of epilepsy in migrainous subjects than would be expected by chance. Such a use of reported findings, ignoring the reservations made, regarding the bias of the sample serves to add to the confusion in this area.

#### 1.9.6 Anticonvulsants as therapy in migraine

Chao, Sexton and Davis (1964) wrote as follows:

"The autonomic disturbances of the convulsive equivalent syndrome have also been considered as a variant of migraine or abdominal migraine. This controversy has by no means been completely settled. The advocates of the epileptic etiology have stressed the following points in their argument ..... (4) the consistently good response to anti-epileptic medication."

Such a statement raises three fundamental questions:

- (a) are all anti-convulsants effective or only some?
- (b) does the mode of action of the effective drugs necessarily imply that epileptic activity must have been present for them to be effective?
- (c) do the anti-convulsants solely have an action of raising the convulsive threshold?

When examining the literature for information on the effectiveness of anti-convulsants, on the one hand there are statements such as that of Alvarez (1959)

"Persons with pure migraine have normal electro-encephalograms, and they are not helped by anti-convulsant drugs."

Yet on the other hand some authors have written favourably on the use of some anticonvulsants, for example, Kellaway, Crawley and Nagawa (1960) writing about children with recurrent abdominal pain (which they felt should be diagnosed as abdominal epilepsy not abdominal migraine - see section 1.9.4) wrote

"Dilantin and diamox alone or together have been found effective in the majority of cases, but other anticonvulsant agents have been used with some success either alone or in combination with dilantin. Meprobamate and the phenothiazine group of drugs have also been used, but without improvement in the patient's symptoms in most cases."

It is Dilantin (also known as phenytoin or diphenylhydantoin) whether alone or in combination with other drugs, which is repeatedly mentioned as having a beneficial effect in migraine or in cyclic vomiting in childhood (abdominal migraine/abdominal epilepsy), (Gibbs and Gibbs, 1951; Livingston, 1951; Millichap, Lombroso and Lennox, 1955; Lennox and Lennox, 1960; Chao, Sexton and Davis, 1964; Graham, 1969; Hall, 1971). This becomes of interest in the light of a paper by Fields and Raskin (1976), to which the reader is referred, who write

"..... pain may result either from activation of specific peripheral receptors or from disrupting normal inhibitory control mechanisms. Standard analgesics, depending on the site of action, may be effective against either type of pain, but anticonvulsants seem most effective against pain arising from dysfunction of the nervous system."

In section 1.7 it was shown that the pain of migraine involves not only pain-sensitizing substances at the periphery but also alterations of central pain perception, such that pain thresholds are lowered.

Fields and Raskin also write

"Present knowledge of the mechanism of action of anticonvulsants at the level of the neuronal membrane is far from complete. Although phenytoin may not be especially effective for the treatment of paroxysmal pain states, it is the most thoroughly studied anti-convulsant. .... These actions of phenytoin on the nerve membrane would be expected to reduce repetitive firing of neurons. If pathological hyperactivity depends on neuronal membrane instability leading to repetitive discharge, phenytoin and other anti-convulsants that have a similar mode of action might act by stabilizing the membrane."

In the light of the discussion in section 1.7 on the serotonin theory and the imbalance between the adrenergic and serotonergic systems, with consequent dysfunction of the hypothalamus, one can speculate as follows. Perhaps the anticonvulsants such as phenytoin act to fill the short-fall of inhibitory action, due to the dysfunction of the serotonergic system, and so reduce the over-arousal of the hypothalamus and other structures served by the serotonergic system, such that they stay within normal limits. Further research upon phenytoin and other anti-convulsants with a similar mode of action, known to be effective in the treatment of disorders of central pain perception would help answer the controversy on whether epilepsy and migraine share a common bio-chemical or electro-chemical basis.

#### 1.9.7 EEG findings of epileptic activity in some migrainous individuals

Bearing in mind all the drawbacks discussed above, some of the EEG studies are invalidated, while others are inadequate (especially on the grounds of a biased sample) for the task of assessing what proportion of the total migraine population display clear evidence of epileptogenic brain activity. However, EEG studies, whether in the form of case reports (Alvarez, 1959; Lennox and Lennox, 1960; Barolin, 1966; Ziegler and Wong, 1967) or in the form of reports on a group of patients (Lennox and Lennox, 1960; Chao, Sexton and Davis, 1964; Barolin, 1966; Slatter, 1968; Hockaday and Whitty, 1969; Ninck, 1970; Poch, 1974), confirm that epilepsy does occur in some migrainous people and some authors have specifically distinguished the following combinations in patients.

- (a) idiopathic migraine and idiopathic epilepsy

(Barolin, 1966)

- (b) idiopathic migraine and symptomatic epilepsy where the seizure occurs at the height of a migraine attack and could be a symptom of the temporary biochemical changes, ischemia or edema that are associated with migraine (Carroll, 1968)
- (c) ideopathic migraine and symptomatic epilepsy where the epilepsy is the symptom of an acquired lesion (Cabral and Scott, 1976) or damage thought to be caused by severe migraine (Barolin, 1966; Ninck, 1970)
- (d) symptomatic migraine and symptomatic epilepsy (Barolin, 1966; Ninck, 1970).

However, Hockaday and Whitty (1969) and Friedman, Rowan and Wood (1974) express some reservations about the epileptogenic effect of repeated migraine, since they could not establish a correlation between a long history of migraine and the presence of paroxysmal activity. Nor could Friedman et al find a relationship between severity or frequency of migraine attacks and the presence of an EEG focus. Thus while symptomatic epilepsy due to a lesion caused by severe migraine is possible, it is by no means inevitable. Details from authors reporting permanent sequelae of migraine attributed to damage to the brain or retina were given in section 1.4.6 and included a report from the Neuropsychology Unit here (Harding, Debney and Maheshwari, 1977) of three children with hemiplegic migraine including one child (who was having frequent attacks) in whom the EEG abnormalities did not resolve, this child continuing to show a focal slow wave abnormality and angiography revealed a local mild abnormality although the brain scan was normal. Thus this child is thought to have a lesion caused by migraine but shows no

evidence of clinical fits or epileptogenic activity.

Of immediate interest to this study are the reports of epileptiform abnormalities in response to intermittent photic stimulation (IPS), although some authors do not give any details of such investigations (Hockaday and Whitty, 1969; Friedman, Rowan and Wood, 1974). Ziegler and Wong (1967) studied 27 children with severe migraine and in a state of sleep deprivation, 4 of these produced paroxysmal abnormalities in response to I.P.S. Lehtonen (1974) reported one of the 33 patients he studied as exhibiting irregular polyspike and wave EEG paroxysms during IPS accompanied by her first syncopal attack of short transitory state of confusion, vertigo and nausea. This female patient was aged 34.

#### 1.9.8 Some conclusions and comments

In the light of the preceeding discussions on the problems of differential diagnosis, adequate definition, appropriate criteria for EEG activity indicating epilepsy, and bias in samples studied, few conclusions can be drawn on the relationship between migraine and epilepsy. For there to be a genetic relationship two conditions should hold. Firstly migraine should occur in epileptics more often than by chance, which in the light of modern population estimates for migraine prevalence, was shown not to occur. Secondly, epilepsy should occur more often than by chance in the migrainous and no clear bias has been shown. Thus one can assume there is no simple genetic linkage but one cannot necessarily assume that the migrainous are not at greater risk of epilepsy than the general population. Furthermore, if they are at greater risk, it has yet to be shown whether any relationship, other than symptomatic epilepsy from severe migraine, would be

sufficient to account for the greater incidence. Friedman et al (1974) point out

"Vasoactive substances also have membrane effects, which suggest that vascular and electrical events may be concomitant and not causal events."

and it is possible such vasoactive substances may alter convulsive thresholds for Scott, Moffett and Swash (1972) have shown that tyramine (see section 1.6. on dietary factors) accentuates paroxysmal EEG features in patients with migraine, especially if there is a concomitant history of seizures. One can speculate whether such effects would result in latent epilepsy appearing as manifest epilepsy in someone whose convulsive threshold would otherwise remain high enough to prevent fits ever occurring. In connection with this speculation a quotation from Kiloh, McComas and Osselton highlights the situation.

"Experience with electro-convulsive therapy has shown that the ability to suffer attacks of grand mal is a universal attribute and the important problem is not so much why so few people have fits but how the majority manage to avoid them." (p. 71).

#### 1.9.9 Photosensitive epilepsy (PSE)

The recent text by Jeavons and Harding (1975), to which the reader is referred, was used as the basic source for much of the information below on both factors precipitating PSE and the associated EEG and evoked potential abnormalities. Jeavons and Harding (1975) suggest an incidence of PSE of 1:10,000, although a recent editorial in the British Medical Journal suggests about 5 per cent of patients with epilepsy are sensitive to light in one form or another, which if the incidence of epilepsy in the population is assumed to be 0.5 per cent would yield a ratio of 1:4,000 in the population. In any event PSE affects a small percentage of the population. Among epileptic

patients showing photosensitivity about 40% have a normal resting EEG record, with paroxysmal activity appearing only to visual activation techniques (Jeavons and Harding, 1975; Editorial British Medical Journal, 1978).

1. Factors precipitating PSE and a comparison with visual stimuli inducing migraine.

The factors precipitating PSE will be considered under the following groupings:- sunlight, artificial light sources; self-induced fits; geometric patterns; colour.

In PSE it is not bright sunlight as such which is reported as a precipitant but situations which produce flickering or fluctuation of the sunlight. These include sunlight shining through the leaves of trees, the interruption of light by the blades of a helicopter, sunlight reflected from snow, or from the waves of the sea, or metal (Gastaut and Tassinari, 1966; Herrick, 1973; Hess, Harding and Drasdo, 1974; Jeavons and Harding, 1975). Flickering sunlight seen when travelling along an avenue of trees, or past railings, has been reported as a precipitant and it is suggested (Jeavons, Harding and Panayiotopoulos, 1971; Jeavons and Harding, 1975) that drivers of cars would not get fits in such a situation as lateral illumination does not evoke abnormal discharges in the EEG during IPS.

Artificial light sources cited as precipitating PSE include oscilloscopes; blades of a mechanical saw; fluorescent lighting; lighting in fairgrounds or amusement arcades; the cinema screen and the television screen (Brausch and

Ferguson, 1965; Gastaut and Tassinari, 1966; Herrick, 1973; Jeavons and Harding, 1975; Editorial BMJ, 1978). Jeavons and Harding (1975) report one patient as 'feeling peculiar' when a pop group switched on a stroboscope and another as 'feeling funny' when travelling past vehicular tunnel wall-lights. Television is the most commonly reported precipitant with most seizures occurring when the set is functioning normally, and a few by loss of stability of the picture or by a change to another channel. The closer the person to the television the more likely a seizure and this is attributable to, firstly, the increasing amount of retina stimulated and, secondly, the resolution of the line details which at close quarters are sufficiently resolved for the 25 Hz pattern oscillation of the lines to take effect whereas at greater distance a 50 Hz flicker effect is produced (Jeavons and Harding, 1975; Editorial, BMJ, 1978). Jeavons and Harding (1975) demonstrated that 25 Hz flicker is more epileptogenic (affecting 85% of 116 patients), than that at 50Hz (affecting 61%).

Self-induced PSE occurs rarely. The patient usually stares at a source of bright light, commonly the sun and waves one hand with outspread fingers rapidly across the eyes (Jeavons and Harding, 1975). No cases of migraine patients inducing migraine in this manner have been reported.

Bickford and Klass (1969) found evidence of pattern sensitivity in 5 per cent of patients sensitive to photic stimulation.



The types of situations involving patterns which had affected some of the photosensitive patients seen by Jeavons and Harding (1975) were listed as:

"..... the steel steps of escalators, windscreen wipers, railway sleepers and posts viewed from the carriage window, bands formed by fluted glass in windows, roof tiles, striped material, a striped garage door of the up-and-over type, a spiromatic toy and the rotating turntable of a record player."

Other authors (Chatrian, Lettich, Miller and Green, 1970; Editorial, New Scientist, 1975) have also listed striped or quadrilled materials, picket fences, wire mesh screens, heater screens, ceiling tiles, bathroom tiles, folding doors, telephone lines in the sky and steps of escalators. Experimental investigations (Bickford and Klass, 1969; Chatrian, Lettich, Miller and Green, 1970; Jeavons, Harding, Panayiotopoulos and Drasdo, 1972; Jeavons and Harding, 1975) suggest patterns are most effective when they are simple, fine, geometric and have a sharp contrast. In addition the effect of the patterns is increased by any of the following conditions, movement of the pattern, macular viewing, and illumination by photic stimulation. Of the different patterns, vertical lines were more effective than angled ones, and Jeavons et al (1972) found a quadrilled or grid pattern to be the most effective, with small squares subtending a visual angle of 22' being the optimum size for producing a photoconvulsive response. Chatrian et al (1970); Editorial, New Scientist (1975), and Jeavons and Harding (1975) refer to the work of Hubel and Wiesel which demonstrates that many cortical neurones respond to contour and contrast and not to diffuse light (this work is considered in more

detail by Morgan, 1965 and Lindsay and Norman, 1972) and Jeavons and Harding comment that it is therefore not surprising that pattern superimposed on light flashes enhances the cortical response.

The literature on the effect of various colours in precipitating photoconvulsive responses is critically reviewed by Jeavons and Harding (1975). They note that, on the one hand, a number of authors report increased sensitivity to red light including Brausch and Ferguson (1965), a finding also reported by Takahashi and Tsukahara (1976) but that, on the other hand, this is not a universal finding. Jeavons and Harding (1975) report their own well controlled study on the effect of colour, in which they controlled the relative intensities of the filtered lights. Half their ten patients showed some increase in their sensitivity range to red light as compared with white light, but as a group there was no significant difference. (The sensitivity range is the range of flashes per second (f/sec.) over which an abnormality can be induced). They also found no significant difference of the group to green light, but a significant decrease in sensitivity range to blue light. Takahashi and Tsukahara (1976) state they kept constant the brightness on the screen of the five coloured lights they used (white, red, yellow, green, blue) but they used only the one flash rate of 15 f/sec. Unfortunately, while they report 7 of their 14 patients as producing a photoconvulsive response to red light, it is unclear whether this is more or less effective than

white light for the group as a whole, although they report one case in whom only red light produced a photoconvulsive response at the tested flash rate. Like Jeavons and Harding (1975) they reported patients were least affected by blue light, and they support the use of blue tinted glasses as a means of reducing sensitivity. The clearest way of comparing the types of visual stimuli reported to affect those with PSE with those reported as inducing migraine is to present them as a table (see Table 1.8). It is immediately apparent that there is considerable overlap in the reports and while some of the situations showing a discrepancy, e.g. sunlight through helicopter blades, are relatively rare in everyday life, other situations showing a discrepancy, e.g. headlights at night, are common. Due to the limited literature on visual stimuli inducing migraine it is possible that some of the blanks in the migraine column should be filled in. This was found to be the case during this study and this table appears in an extended and amended form in section 2 as Table 2.17.

## 2. EEG and evoked potential abnormalities associated with photosensitive epilepsy (PSE)

Hess, Harding and Drasdo (1974) define PSE as:

".... a pathologic entity characterized by sudden recurring seizures precipitated by intermittent visual stimuli. There is a range of frequencies, the photo-sensitive range specific to each patient which can initiate a photoconvulsive response."

Jeavons and Harding (1975) consider that for the diagnosis of PSE one only needs to evoke photoconvulsive responses (PCR) consistently to a number of flash rates and that the nature of the PCR, its duration and the range of flash rates evoking

TABLE 1.8 A comparison of the types of visual stimuli reported to affect photosensitive epileptics with those reported as inducing migraine (see text, section 1.9.9 and section 1.6.10 respectively).

Visual Stimuli	P.S.E.	Migraine
1. <u>Sunlight</u>		
bright sunlight itself		x
through leaves of trees	x	
through helicopter blades	x	
reflected off snow	x	x
reflected off sea or water	x	x
reflected off metal	x	x
reflected off white walls		x
reflected off paper		x
through white clouds		x
travelling down avenue of trees	x	
travelling past railings	x	x
2. <u>Artificial light</u>		
oscilloscopes	x	
stroboscopes	x	x
blades of mechanical saw	x	
fluorescent lighting	x	x
fairground lighting	x	
amusement arcade lighting	x	
cinema screen	x	x
TV screen	x	x
microscopy		x
vehicular tunnels lighting	x	x
headlights at night		x

TABLE 1.8 CONT'D.

Visual Stimuli		P.S.E.	Migraine
3.	<u>Pattern</u>		
	Vertical stripes	x	x
	Horizontal stripes	x	x
	Quadrilled/grid	x	x
	Checkered	x	
	Diagonal stripes	x	x
	Spiral	x	
4.	<u>Colour</u>		
	Red	x	

it are not of diagnostic importance. There is a tendency for authors when reporting photosensitivity to refer simply to PCR (e.g. Brausch and Ferguson, 1965; Takahashi and Tsukahara, 1976) and not to detail the types of PCR that may occur. Jeavons and Harding (1975) distinguish 6 types of PCR as follows, the first type being the most common:

- "1. Bursts of spike and wave activity, usually with a slow component at 3 c.sec.
  2. Bursts of high amplitude theta waves (4-7 c.sec.) with spikes (theta spike and wave).
  3. Bursts of polyspikes or polyspike and wave.
  4. Bursts of spikes at the same rate as the flash, distinguished from occipital spikes" (see below) "by the fact that they extend into the anterior regions.
  5. Discharges of 3 c.sec. spike and wave activity lasting more than 5 seconds after the flashing has ceased, and associated with a clinical absence.
  6. Bilateral high amplitude slow spikes, seen through all regions."
- (p. 59-61)

It is useful to set the PCR in context by briefly considering responses to IPS, Jeavons and Harding (1975) give a useful classification based on the EEG distribution of these responses.

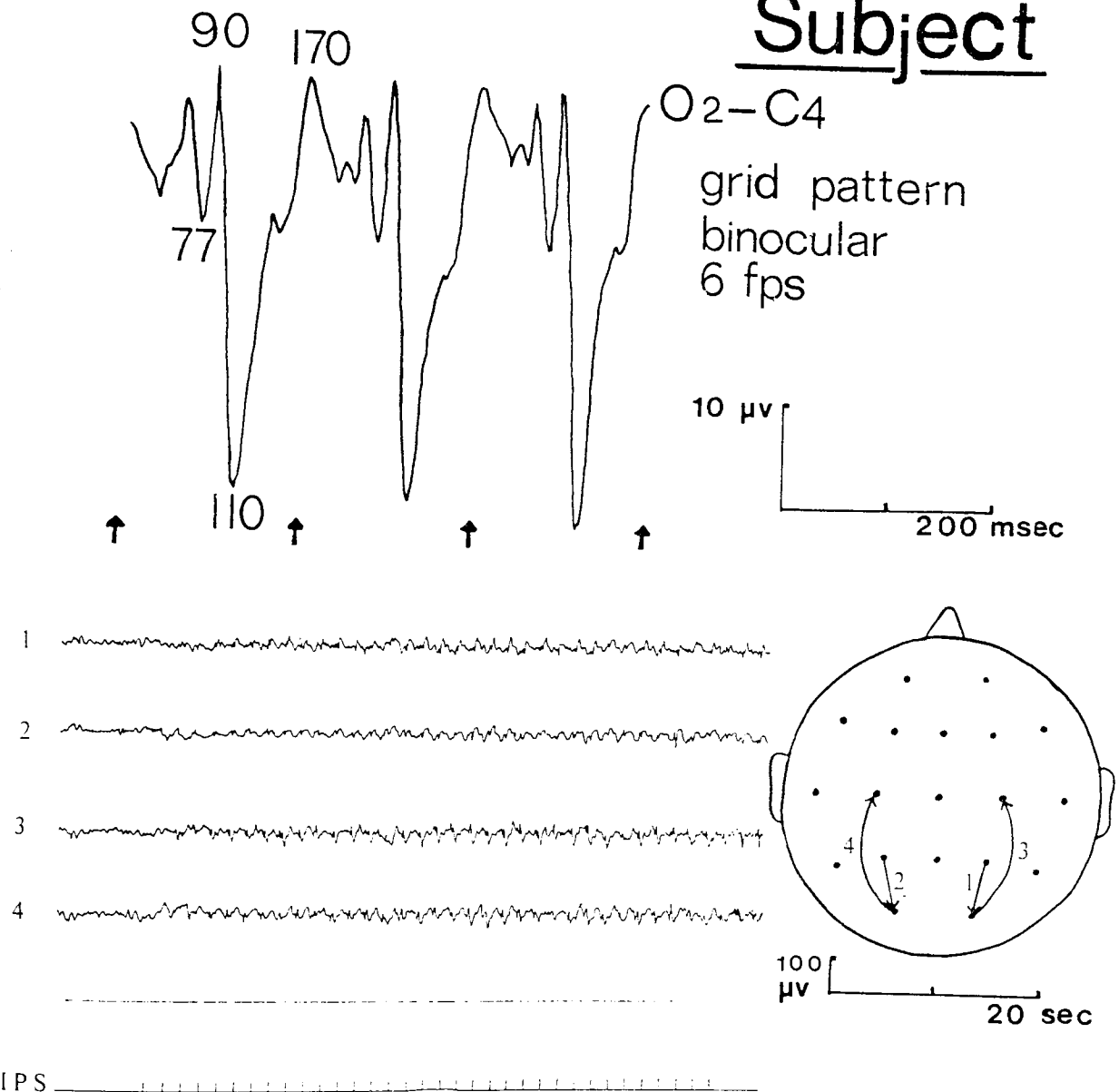
- (a) response seen only in anterior regions: photo-myoclonic responses
- (b) response seen only in posterior regions: photic driving, visual evoked potential (VEP), occipital spikes
- (c) widespread, bilateral response involving anterior and posterior regions: PCR.

The photomyoclonic response consists of frontally predominant polyspikes at the flash frequency accompanied by synchronous jerking (Kiloh, McComas and Osselton, 1972). This response occurs only when the eyes are closed and the light is very bright and very close to the eyes (Jeavons and Harding, 1975). Both these conditions were avoided by Jeavons and Harding in their study of PSE and were avoided in this study, therefore the photomyoclonic response is not considered further.

Photic driving and visual evoked potentials are considered in section 1.8. Rarely, fundamental and harmonic rates of photic driving combine to give a pseudo-spike and wave appearance, which is very similar to negative occipital spikes on visual inspection and can only be clearly distinguished using an averaging computer (Jeavons and Harding, 1975).

Occipital spikes are electro-negative to the occipital electrode and are at the same rate as the IPS. They may precede a PCR or may occur alone. Rarely they are seen in isolation (Maheshwari and Jeavons, 1975) and Jeavons and Harding (1975) are uncertain of the clinical significance in such cases but suggest that seen alone they do not indicate epilepsy (see Fig. 1.5). One of the queries initially raised was whether people with VIM might show occipital spikes either in isolation or with a PCR if migraine were linked with epilepsy as some authors have suggested. Jeavons and Harding (1975)

# E.E.G. & V.E.P. Normal Subject



J.P. 25 yrs M.

FIG. 1.5 This young man had volunteered as a control subject for the pilot study (Debney, 1973). He had no personal or family history of epilepsy and had never found flickering light to be unpleasant. He showed occipital spikes to IPS in the range 4 to 8 f/sec. when a grid pattern was in position in the stroboscope but not to unpatterned flashes. No PCR was evoked. The VEP shows an occipital spike at 90 msec. which is characteristic of occipital spike in PSE (see Fig. 1.6).



studied occipital spikes in the EEG and distinguished the following characteristics:

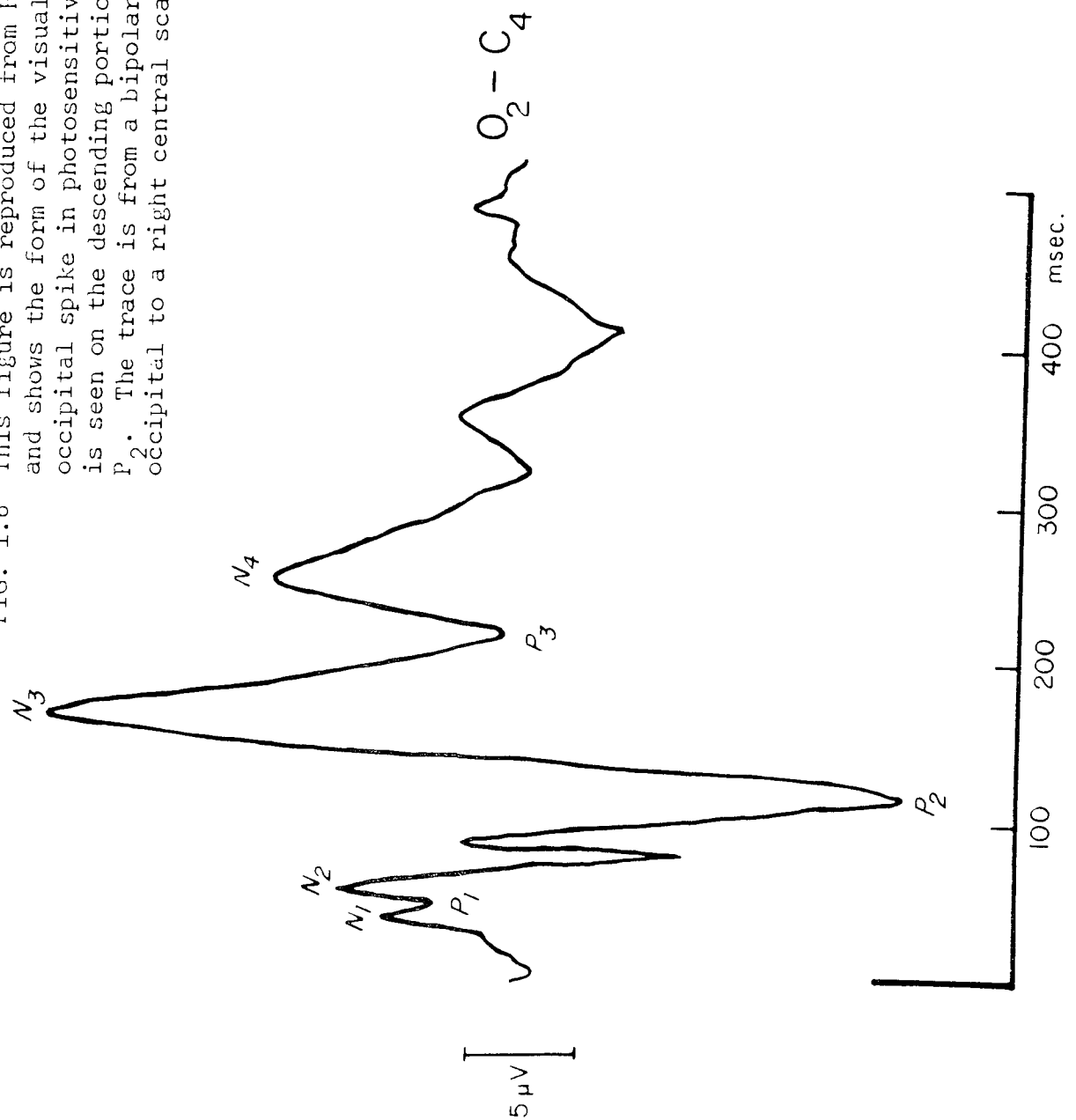
- (a) they appear in the EEG between 200 m.sec. and 3 seconds after the onset of IPS but never appear in response to the first flash
- (b) As the flash rate increases the first occipital spike tends to occur earlier.
- (c) In most patients the occipital spikes progressively increase in amplitude in response to subsequent flashes, reach a maximum after 3 to 9 flashes, then either decline in amplitude (which generally occurs at lower flash rates, i.e. 5 to 7 f.sec.) or end in a PCR (seen at higher flash rates within their photosensitivity range).
- (d) Occipital spikes are fundamentally related to the flash rate in the majority of patients.
- (e) Amplitude of negative occipital spikes was usually between 60 and 100 $\mu$ V. but was occasionally 150  $\mu$ v.
- (f) They are usually symmetrical in the two hemispheres.
- (g) Monocular stimulation is less effective than binocular in producing occipital spikes and in the eyes closed condition, they are also less easily produced and usually disappear.

Occipital spikes were seen in the EEGs of 64% of PSE patients studied by Jeavons and Harding (1975) but using an averaging computer they found an occipital spike in the VEPs of nearly all photosensitive patients (in section 1.8 it was discussed how the 'noise' of the EEG can conceal the 'signal' of the

visual evoked response). In contrast to earlier suggestions occipital spikes were found not to be an augmentation of one of the early negative components of the VEP but to occur at a latency which means they appear to develop from the  $P_2$  component of the VEP (see Fig. 1.5) and increase in amplitude with increasing flash rate. The negative occipital spike generally appeared on the descending portion of the  $P_2$  component and showed a mean latency of 91 m.sec. (standard deviation 3.5 m.sec.), this latency and that of the  $P_2$  component of the VEP remained consistent in each patient irrespective of the flash rate. (An example is given in Fig. 1.6). Jeavons and Harding (1975) noted the combination of a diffusion screen, a fine grid pattern and high intensity light is a highly provocative stimulus for photosensitive patients and produced occipital spikes at below 8 f.sec.

Hess, Harding and Drasdo (1974) consider the pathophysiology of PSE and Jeavons and Harding (1975) restate the general conclusions. These are that occipital spikes appear to be affected by the same factors which affect the normal physiological responses of photic driving and the VEP (i.e. pattern, intensity, direction of gaze, monocular or binocular stimulation). Secondly, that if the positive  $P_2$  component of the VEP is produced by inhibitory post-synaptic potentials, as suggested by Creutzfeldt and Kuhnt (1967) then the similarity of the latencies of the occipital spike and the  $P_2$  component could be regarded as a failure of normal inhibitory mechanisms in the visual

FIG. 1.6 This figure is reproduced from Hess, Harding and Drasdo (1974) and shows the form of the visual evoked potential (VEP) and occipital spike in photosensitive patients. The occipital is seen on the descending portion of the curve between  $N_2$  and  $P_2$ . The trace is from a bipolar recording from a right occipital to a right central scale electrode.



cortex. Finally, Jeavons and Harding (1975) suggest the occipital spike may act as a temporary epileptogenic focus in precipitating the PCR.

Earlier in section 1.7 the serotonin theory of migraine was discussed and this suggests lack of MAO causes reduced monoamine turnover, which is compatible with reduction of the activity of the serotonergic nervous system which is thought to exert an inhibitory action. Moreover some of the serotonergic system projections go to the visual cortex, where they presumably exert an inhibitory influence. Thus if occipital spikes are assumed to reflect some failure of natural inhibitory mechanisms and they were to be consistently found in the patients with visually induced migraine, a tentative explanation would be available in terms of the reduction of the inhibitory action of the serotonergic system.

### 1.10 Migraine and EEG and VEP findings

An excellent review of the EEG in migraine has been made by Parsonage (1975) to which the reader is referred. The main points of his review are summarized below along with his main conclusions. His review of the basic EEG and hyperventilation responses is generally adequate for the purposes of this study and is substantiated by papers read in addition to those he reviewed. However his coverage of the response to intermittent photic stimulation (IPS) is too limited for the purposes of this study and he does not cover evoked potential studies, both of which are considered below. Reference will also be made to other sections including 1.9 on Migraine and Epilepsy.

Parsonage finds that investigations of EEG abnormalities have focussed on the following:

- (a) Ictal abnormalities (during the attack) and inter-ictal abnormalities (headache-free periods).
- (b) Abnormalities in particular varieties of migraine (e.g. hemiplegic migraine).
- (c) Changes seen in rare cases with signs of permanent cerebral damage.
- (d) Attempts to define a particular type of migraine on the basis of EEG criteria ("dysrhythmic" migraine).
- (e) Responses to specific stimuli, e.g. flicker.
- (f) Responses to pharmacological agents.
- (g) Investigations of the suspected relationship between migraine and epilepsy.

The more important of the EEG changes are summarized in Table 1.9. Parsonage stresses that caution must be exercised when interpreting the literature for (as mentioned in section 1.9), not only have the reported investigations been carried out almost exclusively on patients referred to clinics (i.e. those with the more intractable forms of migraine) but also there has often been further selection when carrying out EEG investigations (e.g. Barrios, 1961; Hockaday and Whitty, 1969). This bias in the sample studied will influence the estimates of the incidence of EEG abnormalities associated with migraine, which are usually in the range of 25 to 55 per cent (e.g. Selby and Lance, 1960; Hoefer, 1967; Heyck, 1969; Domzal, 1975; Goldensohn, 1976). In contrast Parsonage puts the expected incidence of abnormalities in the general population as 5 to 10 per cent although others (Hoefer, 1967; Rowan, 1974) put it at about 15 per cent. Moreover Giel et al (1966) suggest that in any sample of patients, one can find at least 20% of cases with an abnormal EEG.

Although Parsonage states that authors agree about the types of changes seen but not about their significance, he does not explicitly say that disagreement extends to criteria of abnormality. For example, on the one hand Boudin, Pepin, Barbizet and Masson (1962) write that they found only 8 frankly abnormal records in migraine patients over a period of 5 years and that:

"As a rule the EEGs of patients with migraine which we have recorded were normal or subnormal, characterized either by:-

- (a) the richness of diffuse beta rhythms
- (b) the spiky or wicket aspect of the alpha rhythms
- or (c) the presence of disseminated theta rhythms which are also numerous."

**TABLE 1.9** Patterns of the more important EEG changes as distinguished by Parsonage (1975) from the literature, with an addition.

Resting Record	Interictal		Ictal	Effects of Pharmacological Agents
	Hyperventilation	Photic Stimulation		
<p>1. Abnormal slow wave activity (1-7 f/sec.) most commonly generalised, less commonly focal or both.</p> <p>Posterior quadrant slow wave abns.</p> <p>2. "Dysrhythmic" migraine - paroxysmal slow activity, 6-8 c/sec. "spindles", random sharp waves.</p> <p>3. Paroxysmal activity, slow waves, spikes, sharp waves, spike-waves - may be generalised or localised.</p>	<p>1. Excessive slow wave response, accentuation of resting record abns.</p> <p>2. Marked "activation" in all cases of "dysrhythmic" migraine.</p>	<p>1. Extension of response to flash rates above 20/sec.</p>	<p>1. Transient focal slow activity accompanying aura with focal signs.</p> <p>2. Rarely, persistent focal abns.</p> <p>3. "Exaggeration" of interictal abn.</p> <p>4. Activation of pre-ictus patterns in "dysrhythmic" migraine.</p>	<p>1. Increase of abn. slow activity after i.v. ergotamine.</p> <p>2. Abolition of focal 1-3 c/sec. by inhalation of CO<sub>2</sub>.</p> <p>3. In "dysrhythmic" cases good response to anti-convulsants but little or none to ergotamine.</p> <p>4. Tyramine augments pre-existing abnormalities (Scott et al, 1972).</p>

In contrast Selby and Lance (1960) concluded that the theta activity persistent or occurring in runs, was beyond the range of normal in 122 (26.2%) of 459 patients and this accounted for the majority of the 137 (29.8%) abnormal records reported. The other abnormalities being asymmetrical slow activity in 15 (3.2%) and spike and wave paroxysms in 2 (0.04%). It should be noted that the figure of 0.04% agrees with the text and the figure of 0.4% given by Selby and Lance in their table is presumably a misprint. A further contrast in criteria of abnormality is seen in the report by Ulett, Evans and O'Leary (1952) on the EEG findings in 1,000 patients with the chief complaint of headache. Their criteria of an abnormal record included fast activity occurring during 40% of the record, as well as slow activity of less than 7 c/sec exceeding 50 microvolts and paroxysmal records. Of their 1,000 cases, 15.8% were considered to have abnormal records. Three hundred and ten of their patients had unilateral headaches and in these 15.2% of the records were abnormal. In those with unilateral headache accompanied by vomiting 18% of the records were abnormal.

Wolff (1963) reported the distribution of normal and abnormal records for patients with the complaint of headache of any kind and the distribution for the headache-free population to be approximately the same. However he found that patients with vascular headaches of the migraine type had an incidence of abnormal EEGs that was twice as high as that of the controls, and that in these cases slowing was the main abnormality. This finding is in line with those above.

Camp and Wolff (1961) investigated the significance of the focal slow wave abnormalities and distinguished three types of delta and theta



(1 to 7 c/sec.) foci.

1. that appearing with the onset of clinical symptoms and disappearing when the symptoms resolved. This was considered likely to reflect local vasoconstriction and cerebral ischemia. This corresponds to the first of the ictal changes in Table 1.9 and examples in the literature include changes accompanying visual loss (Engel, Ferris and Romano, 1945; Connor, 1962) and non-familial hemiplegic migraine (Whitty, 1955), both described in section 1.4.6.

Support for the hypothesis of vasoconstriction producing ischemia and so the EEG changes comes from the observation that the vasoconstrictor drug, ergotamine, when introduced intravenously, increases the abnormal slow wave activity (Dow and Whitty, 1947).

2. Focal abnormalities lasting hours or days were suggested to be related to oedema. Such abnormalities outlast the headache and would account for at least a portion of the first of the resting record changes in Table 1.9. A variety of persisting symptoms were described in section 1.4.6. Slatter (1968) describes posterior quadrant slow waves as usually bilateral, but generally more marked on the side causing the major visual symptoms. Slatter also reported transient generalised slow activity seen shortly after an attack of basilar artery migraine. The most thoroughly investigated persisting symptom is hemiplegia. In such hemiplegic migraine cases the abnormalities may be generalized but are more often predominantly or exclusively lateralised to

the appropriate side and show a gradual reduction in abnormality over the following days or weeks (Clarke, 1910; Whitty, 1953; Connor, 1962; Bradshaw and Parsons, 1965; Pearce and Foster, 1965; Carroll, 1968; Slatter, 1968; Bruyn, 1969; Verret and Steele, 1971; Beck and Manz, 1972; O'Connor, 1973; Dooling and Sweeney, 1974; Boisen, 1975; Gastaut, Giraud and Saint-Jean, 1975; Glista, Mellinger and Rooke, 1975; Pearce, 1975b; Johnson, 1976; Harding, Debney and Maheshwari, 1977).

3. Long lasting abnormalities which appear to be the result of infarction. Parsonage lists these under ictal abnormalities as 'rarely, persistent focal abnormalities' but some can be considered permanent (Murphy, 1955; Connor, 1962; Wolff, 1963; Friedman and Pampiglione, 1974). Some examples are given in section 1.4.6.

Of the 459 recordings made by Selby and Lance (1960), 137 (30%) were judged abnormal and the great majority of these were accounted for by 4-7 c/sec. activity occurring persistently or in runs (122 records) but the relation of these to symptoms or date of last headache is not given, indeed this information is seldom given by authors. Such information would help in the assessment of the significance of such slow wave activity, especially if serial recordings were obtained.

The other condition involving slow wave abnormalities in Table 1.9 includes the response to hyperventilation. Slatter (1968) found pre-existing EEG abnormalities or asymmetries were accentuated by hyperventilation some abnormalities were seen only during hyperventilation and the slow wave response to hyperventilation was

markedly reduced by giving glucose. Supporting these findings are the reports of Friedman and Pampiglione (1974) and Goldensohn (1976). Towle (1965) suggested the significant slow wave exaggeration in hyperventilation was a result of the vasoconstriction and thus reduced cerebral blood flow, produced by lowered arterial  $p\text{CO}_2$  and wondered if the migrainous had chronic  $p\text{CO}_2$  sensitivity. The role of the  $p\text{CO}_2$  is supported by the observation of Smyth and Winter (1964) who found inhalation of  $\text{CO}_2$  could completely relax the cerebral vessels and such inhalation was associated with the disappearance of 1 to 3 c/sec. slow EEG activity. They suggested the mechanism of migrainous headache is related to the homeostatic processes responsible for the regulation of cerebral circulation. It is difficult to better Parsonage's summing up of the interpretation of the hyperventilation responses and it is therefore quoted below:

"It is generally accepted that the EEG generalised slow wave responses induced by hyperventilation reflect ischemia consequent upon reduced cerebral blood flow which in turn is related to hypocapnic constriction of cerebral blood vessels. It is important to remember that this type of response shows wide variation in normal individuals and is often particularly marked in young subjects. Furthermore, there is much variation in the way in which patients routinely carry out this procedure and the response is sensitive to quite small changes in blood sugar level. It is clear therefore that much care is required in the interpretation of an overbreathing response that is generalised and symmetrical. Nevertheless, it seems to have been established that migrainous subjects as a group are apt to exhibit instability under the stress of hyperventilation but this is not confined to migraine."

Parsonage reports that 'dysrhythmic' migraine was originally reported by Cohn in 1949 and this concept developed by Weil (1952, 1962). In this 'type' of migraine Weil distinguished two types of abnormality, both of which were typically diffuse but showed 'focal accentuation' in 37 per cent of cases. These two interictal abnormalities, which might occasionally appear concurrently, were high voltage slow wave paroxysms in the EEG and high voltage 6 to 8 c/sec. 'spindles'

and sporadic spikes. The most consistent feature was marked hyperventilation activation which was seen in all cases and a similar sort of activation was said to occur during attacks. Weil thought the excessive hyperventilation response might reflect incompetent homeostatic mechanisms and sensitivity of cerebral neurones to low  $\text{CO}_2$  tension, which agrees with the discussion above. Weil also reported ergotamine preparations to be of little use in such cases if given alone and that a marked therapeutic improvement occurred if phenytoin or methoin were added.

Parsonage considers it significant that Slatter (1968) stated he had observed all variants from episodic theta activity to the dysrhythmic picture of mixed slow and fast rhythms, these being either variable or constant. Parsonage concludes that so-called dysrhythmic migraine remains an enigma and that he, like many others, finds it is not easy to define on clinical grounds and the EEG appearances are not sufficiently distinctive to justify classifying it as a special variety. He adds:

"Nevertheless, more attention might be given to the use of anti-convulsants in the more florid examples of this type of syndrome".

The literature suggests that it is not anticonvulsants in general which are successful in migraine but rather mephenytoin (Friedman and Colin, 1951) and, in particular, phenytoin (see section 1.9 where some comments were made on the possible modes of action of phenytoin and the need for research into its efficacy in migraine).

Section 1.9 considered literature on a possible relationship between migraine and epilepsy. Parsonage also concludes that it has not yet

been established on either clinical or EEG grounds that migraine and epilepsy have a common constitutional basis. In migraine patients studied epileptic phenomena may occur more often than expected by chance, how much this is related to the selection of patients, the cause of migraine or caused by migraine has yet to be determined (see section 1.9). Parsonage notes that focal spikes or sharp waves associated with slow waves may develop following focal migrainous aura and that these may be seen in the absence of epileptic manifestations and suggests this may mean a potential liability to epilepsy has developed, although some additional change may be necessary before it can be overtly expressed. Parsonage continues (a point not raised in section 1.9) that this situation may be comparable to some cases of cerebral atherosclerosis in which sharp wave activity is seen in the EEG, especially in the temporal regions in the absence of manifest epilepsy. A view substantiated by Scott (1976) who writes that inter-ictal migraine records can show disorganized background activity and episodes of fronto-temporal theta waves, the components often having a sharp outline and resembling older subjects with diffuse cerebrovascular disease. Ninck (1970) noted that of the 591 migraine patients he studied 13 had idiopathic migraine with focal epilepsy and of these 10 had temporal lobe paroxysmal discharges. His explanation of this preponderance is that it is well known that the blood supply is less abundant in the temporal lobes than elsewhere in the brain and that therefore they are less resistant to ischemia. Presumably this vulnerability accounts for the findings in cerebrovascular disease as well as those attributed to migrainous ischemia. Further support for the relative vulnerability of the temporal lobes in migraine comes from Rowan (1974) and from Friedman and Pampiglione (1974) who noted that when excessive sharp

elements (but not spikes) appear in the EEG record of migraine patients they are most obvious in the temporal or paracentral regions.

Parsonage did not report the findings by Scott, Moffett and Swash (1972) that oral tyramine (a dietary precipitant of migraine, see sections 1.6 and 1.7) activates pre-existing EEG abnormalities in a significant number of patients with dietary migraine and in those with migraine and epilepsy but not those with migraine alone. Since this effect occurred in the absence of headache and also the migraine and epilepsy group did not recognize diet as a precipitant, it is difficult to interpret such a finding as the tyramine precipitating an attack and thus producing the ictal exaggeration of abnormalities observed by Dow and Whitty (1947). Scott et al (1972) suggest the effect of tyramine in epileptic patients warrants further investigation, and Rowan (1974) extends this suggestion to the electrochemical effect of tyramine in both migraine and epilepsy.



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Parsonage suggests that following further research should:

- (a) Determine the incidence of EEG abnormalities in migraine in more representative samples of the migraine population.
- (b) Clarify the significance of the instability of EEG appearances during hyperventilation.
- (c) Seriously question the existence of a link between migraine and epilepsy in the light of the confusion in the literature (see section 1.9) and determine to what extent paroxysmal activity in the migrainous is a chance association, reflects a common cause or is caused by the migraine.
- (d) Investigate the usefulness of anticonvulsants in migraine.
- (e) Investigate the significance of the extended range of responses to flicker.

Parsonage dealt only briefly with the responses to photic stimulation and did not mention the occasional paroxysmal response (PCR) to IPS seen in some of the migrainous (see section 1.9). Of the authors using photic stimulation some do not make any specific mention of any PCR in their large number of patients, that is Hockaday and Whitty (1969) with 560 migraine patients, Friedman, Rowan and Wood (1974) with 150 migraine patients and Rowan (1974) with 220 migraine patients. Conversely others do not specify their number of patients but do say all responses to photic stimulation were normal (Boudin et al, 1962; Domzal, 1975). As migraine is a common disorder reports of some patients referred with PSE also having migrainous headache are not unexpected (Brausch and Ferguson, 1965; Jeavons and Harding, 1975). Of more immediate interest are the reports of paroxysmal responses to IPS in migraine patients, as PSE is a relatively rare condition (see section 1.9). Where incidence figures

are given for such abnormalities in migraine patients these are higher than would be expected by chance but again the bias to be found in migraine patients referred to clinics might influence this. Barrios (1961) stated 6.8% of 72 selected cases of migraine from 250 patients attending a hospital showed an abnormal reaction to photic stimulation. Bille (1962) found 3 of 72 migrainous school-children and 3 of their matched controls showed abnormality to IPS, in this case these were reported to occur mainly with rapid flicker frequencies, usually in connection with eye closure and occurred as a short run of high amplitude subharmonic waves, these could be a form of PCR (see section 1.9.9), no comment is made about resting EEG abnormalities in these cases. Richey et al (1966) report 2 out of 46 migrainous patients as having spike and wave in the resting record and in response to IPS, but as having no history of seizures. Ziegler and Wong (1967) found a higher incidence of abnormality for 3 of the 27 patients showed epileptiform discharges to IPS in the absence of hyperventilation, but the state of sleep deprivation may have influenced susceptibility. Barolin (1970) remarks on striking reactions to hyperventilation and flickering light which sometimes produce paroxysmic discharges in the EEG but gives no details. A much lower incidence is given by Slatter (1968) who found that one case in 174 migraine patients exhibited spikes and slow waves to IPS. Lehtonen (1974) also found one such case, (with no history of seizures) in 33 patients. Friedman and Pampiglione (1974) studied 160 migrainous children and found 8 to have irregular spike and slow wave responses to IPS, 2 of whom had no such abnormalities in the resting EEG. Finally, Goldensohn (1976) gives no figures but includes an example of an off response PCR found in a migraine patient. Such reports as these raise the questions of whether the



seemingly high incidence of PCRs in the migrainous is purely fortuitous, and also, in the light of earlier discussions on visual precipitants, whether those reporting VIM might be the ones to exhibit such abnormal responses.

A common finding in the migrainous, according to the literature, is a more extended photic driving response, i.e. photic driving continues to be seen at higher flash rates. The original study by Golla and Winter (1959), arose from an observation by Winter. Patients at the Burden Neurological Institute were routinely exposed to IPS from a stroboscope lamp and Winter formed the impression that a large proportion of the subjects responding predominantly at high stimulus frequencies, without showing subharmonics or paroxysmal discharges, were those complaining of headache. To investigate this further a special apparatus was constructed to vary the flash rate systematically over the range 6 to 24 flashes per second (f/sec.). Starting with 6 f/sec. each flash rate was held for a 10 second period, and increased by 2 f/sec. every 10 seconds. Thus the whole range was covered in 10 steps during a period of 100 seconds. The results were obtained in the eyes closed condition from the temporo-occipital derivation yielding the highest response to flicker and were quantified using a Walter Mark II analyser. A graph obtained representing the amount (or average amplitude) of the photic driving response at each frequency. From these graphs they distinguished three types of response (see Fig. 1.7). Firstly the 'H' response in which the response is maintained continuously above 14 f/sec. up to or above 20 f/sec. Secondly the 'N' response in which the response curve of the normals falls away above about 14 f/sec. Finally two of the 35 normals showed a second distinct peak of response at a frequency

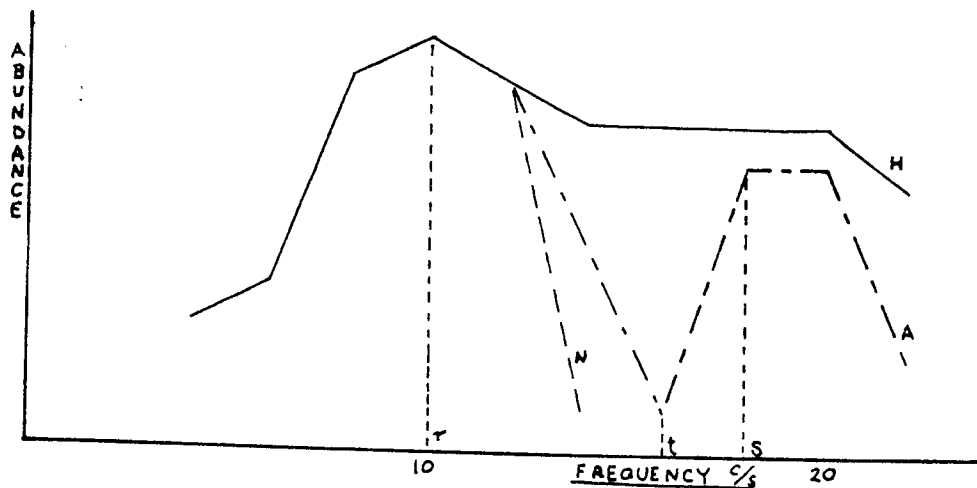


FIG. 1.7 Three distinct types of response curve found by Golla and Winter (1959) as described in the text. They designated these as:

- N - normal curve found in subjects without headache, with a peak in the alpha band and declining rapidly with increase of stimulus frequency above 14 f/sec.
- H - migrainous curve found in patients complaining of migrainous type headache, with a flat top showing a response maintained up to or above 20 f/sec.
- A - third type of curve found in a few patients in control group; this showed a peak in the alpha band, a trough at about 14 f/sec. and a second peak at about 18 f/sec.

The three different types of curve can be differentiated by direct comparison of the abundance of response at 18 f/sec. (s) with that at the peak (r), and of the abundance at the trough (t) to that at 18 f/sec. (s).

i.e. 1. to differentiate N from A and H curves

$$\text{If } \frac{\text{the response at 18 f/sec. (s)}}{\text{the peak response (r)}} > \frac{1}{3} \text{ then}$$

the curve is an A or H type.

2. to differentiate H from A curves

$$\text{If } \frac{\text{the response at the trough (t)}}{\text{the response at 18 f/sec. (s)}} > \frac{1}{2} \text{ then}$$

the curve is an H type.

higher than 14 f/sec., thus producing a trough in the curve at about 14 to 16 f/sec. and this was termed the 'A' response. Those migrainous with an H response tested during an attack or while receiving oral medication showed no significant alteration of their H response. Later Smyth and Winter (1964), whose diagnostic criteria for migraine were given in section 1.3, reported they had observed the H response in 95 per cent of a series of 202 patients with migraine, 20 per cent of 996 individuals with other complaints (including epilepsy 496, syncopal attacks 177, tension headache or psychoneurosis with headache 144, post-concussional syndrome 97, cerebral tumour 42, miscellaneous 40) and in 14 per cent of 66 normal adult volunteers. They did find a significantly high incidence of the H response (66 per cent) in the 97 cases with head injury.

Townsend (1967) used a flickering stimulus similar to that of Golla and Winter but fed the EEG from the right occipital region together with a train of pulses representing the stimulus flashes into an Elliot Tandberg FM tape recorder for subsequent analysis by a digital computer to yield averaged responses to different flash rates (6 to 31 f/sec.) and graphs of amplitude plotted against frequency. He also distinguished H, A and N type curves but gave no incidence figures for them in the migraine patients or controls. In addition he noted the averaged responses could be well replicated using pure sine waves at the fundamental and second harmonic frequencies although the H response was best shown in the graph of the amplitude-frequency graph of the fundamental component. He concluded:

"It seems then that there are interesting variations in the amplitude of fundamental and harmonic sinusoidal responses to rhythmic flicker stimuli, which may be important indicators of the activity of some mechanism whose malfunction is related to attacks of clinical migraine. Smyth and Winter associate the H-response with 'instability of the control system relating vascular tone to cortical activity'".

This is similar to the view expressed by Slatter (1968) who described the flicker responses found in 174 patients with migraine attending a neurological department. He observed that 150 (86 per cent) of these showed obvious following in the EEG to over 20 f/sec. and regarded this following as a characteristic and important feature of the total clinical picture. He noted the photic driving was commonly more marked with the patient's eyes open than closed, and in some only occurred with the eyes open. The responses to higher frequencies (over 20 f/sec.) tended to be smaller than those to lower rates and more difficult to see in the raw EEG. In some patients a Faraday BNI wave analyzer using direct write out facilities was used to quantify the responses in the post temporo-occipital derivation(s). This made it easier to see not only responses to higher flash rates but also harmonic responses (usually double or half the flash frequency) observed in the EEG trace and these responses were seen to vary from moment to moment.

In contrast to the high incidence of the H response in migraine patients found by Smyth and Winter (1964) using automated analysis and by Slatter (1968) with visual observation, Friedman and Pampiglione (1974) with visual observation found an extended flicker response in 73 (46 per cent) of 160 migrainous children and Domzal (1975) in only 25 per cent of 100 patients. Bille (1962) did not have automated analysis available to compare the responses to IPS in 73 children with pronounced migraine to 73 control schoolchildren so he used a rating method to examine waves occurring at the same frequency as the IPS. Driving of subharmonic rhythms was also observed but such responses usually occurred episodically and were included under the heading of episodic and paroxysmal phenomena. The rating method was

to examine the responses of about 15 f/sec. or more and rate them as:

- grade 0 - basic pattern not influenced at all by flickering light
- grade 1 - rare or only sporadic driving response
- grade 2 - driving effect fairly pronounced
- grade 3 - driving constant through the frequency range.

He found some degree of driving occurred in 92 per cent of the migraine children as compared to 77 per cent in the controls, the difference being probably significant ( $p < 0.05$ ).

Parsonage concludes that the precise significance of the flicker responses seen in migraine remains uncertain. Although often seen in migrainous individuals it is not exclusive to the condition, and is seen in some apparently normal individuals. Ulett, Gleser, Winokur and Lawler (1953) showed a significant tendency for the anxiety-prone to show a similar increase in the extent of photic driving, with this being especially marked in to 20 to 30 f/sec. range. This is of interest for migrainous individuals as a group tend to be more tense and anxious than the population generally (see section 1.6.3). Moreover, some authors have commented that migrainous patients show excessive fast (beta) activity in their EEGs, (Ulett et al, 1952; Boudin et al, 1962; Friedman and Pampiglione, 1974) and, such faster than normal activity is seen when, for physiological or pathological reasons, cerebral activity is increased beyond the basic state and it is found as a diffuse change in states of tension or anxiety. Furthermore Montagu (1967) when investigating photic driving in the eyes open condition and using a BNI wave analyzer concluded that the more prominent the faster

rhythms in the basic EEG the greater tended to be the responses at 20 to 24 f/sec. A statement supported by the earlier observations of Hughes (1960). Thus the photic driving response seen in the migrainous may be only indirectly associated with migraine and directly associated with cerebral arousal. In section 1.7 the serotonin theory of migraine was discussed and it was suggested that the reduced functioning of the serotonergic nervous system would be compatible on the one hand with apparent over-activity of the sympathetic nervous system, and on the other hand, through projection to the cortex, with lack of inhibition (i.e. over-arousal) of the cerebral cortex.

Only four studies examining the visual evoked potential (VEP) components in detail have been discovered (Richey, Kooi and Waggoner, 1966; Regan and Heron, 1970; Lehtonen, 1974; MacLean, Appenzeller, Cordaro and Rhodes, 1975). VEPs evoked by simultaneous stimulation of the left and right half fields can be separately identified and measured, and Regan and Heron (1970) found that in normal subjects, the potentials evoked by stimulation of the right or left half fields do not differ by more than 50% from those resulting from simultaneous stimulation of both fields. However, patients with migraine showed a greater than 50% difference in 3 out of 5 cases. Regan and Heron do not say if these three usually had visual aura. By comparing responses to pattern and intensity stimulation, they were able to predict a hemianopia with macula sparing in one case, and this prediction was subsequently verified by perimetry (this case was reported separately by Regan and Heron in 1969). MacLean et al (1975) studied flash evoked potentials in 4 classical migraine patients with a history of lateralized visual aura, 4 patients with

common migraine and 5 non-migrainous controls. During the visual aura of scotoma other workers had noted changes in the raw EEG (see above) and MacLean et al found the hemisphere contralateral to the field defect showed suppression of three VEP components ( $P_1$ ,  $N_1$  and  $P_2$ ). In two of these patients asymmetries were noted during headache free intervals also. Patients with common migraine could not be differentiated from controls either during an attack or while headache free.

Neither Richey et al (1966) nor Lehtonen (1974) noted any difference between the responses of those with the classical and those with the common type of migraine between attacks. Lehtonen (1974) found no significant differences between migrainous and controls in the latencies of VEP components recorded in the eyes open condition to 0.8 f/sec. but found amplitude differences with  $N_1$  being higher and  $N_3$  lower in the migrainous (but not significantly so) and  $P_1$  significantly larger ( $p < 0.05$ ) when measured from the left occipital electrode to a non-cephalic electrode. Eight faster flash rates from 3.7 to 50 f/sec. were used and while responses to each of these tended to be larger in the migrainous the difference only reached statistical significance at 22 f/sec. ( $p < 0.05$ ). This was the only rate to fall within the beta range of frequencies and as such this reinforces the findings on the extension of photic driving discussed above. However, Lehtonen reported considerable overlapping of his findings with some migraine patients showing small and some control subjects high responses at 22 f/sec. This reinforces the above conclusions that an extended photic driving response is neither exclusive to the condition nor absolutely characteristic of migraine but that a trend towards such a response exists in the migrainous.

An earlier study by Richey et al (1966) examined VEPs to flashes slower than 1 f/sec. in 50 migraine patients and 46 control subjects. Unlike Lehtonen (1974), Richey et al found differences in the latencies as well as amplitude in the VEPs from the occipital electrode (a non-cephalic reference electrode was used).  $N_2$  was found to occur slightly later ( $p < 0.002$ ) in the migrainous and in females  $P_1$  was later in the migrainous. In contrast to Lehtonen the only amplitude change found was a reduction of  $P_2$  ( $p < 0.005$ ). Had this reduction been found by both authors this would have fitted well with the suggested reduction of cerebral inhibition arising from reduced functioning of the serotonergic system, as Cretuzfeldt and Kuhnt (1967) suggested  $P_2$  and  $P_3$  represented post-excitatory polarization (inhibition) and a reduced  $P_2$  would thus represent reduced inhibition. Unfortunately the studies by Richey et al (1966) and Lehtonen (1974) show no agreement regarding latency or amplitude changes and therefore such speculation is premature. It is unclear to what extent the differences in the findings by Richey et al (1966) and Lehtonen can be attributed to lack of control of certain factors and to differences in technique. Both authors report their control groups as having the same average age as the patients, but a similarity of averages does not necessarily mean compatibility between groups for the age ranges and it is suggested adequate age and sex matching of control groups is needed (see section 1.8). The technical differences between the authors include electrode placement and stroboscope distance. Richey et al (1966) placed the stroboscope 5 cm. from the subject's face and Lehtonen (1974) 40 cm. from the subject's face, the relative sizes of the stroboscopes cannot be compared. Finally, there was a marked difference in pupil sizes (see section 1.8) with Lehtonen (1974) dilating the pupils of all his subjects (which kept this variable



constant). In contrast Richey et al (1966) did not tamper with pupil size, but measured it immediately before and after stimulation and found the migrainous to have significantly smaller pupils than the controls ( $p < 0.001$ ). Small pupil size, by reducing the amount of light falling upon the retina, might affect the VEP in a consistent manner (see section 1.8).

Taken in a broader context this finding of small pupil size is of interest. In the light of the literature review in sections 1.6 and 1.7 two predictions could be made. On the one hand evidence suggests the migrainous show an over-active sympathetic nervous system (SNS) and with dominance of the SNS one would expect to find a greater dilation of the pupils (Morgan, 1965) than in controls, but the reverse is true. On the other hand Herberg (1975) suggested bright light might act by inhibiting pineal melatonin, which is able to raise the serotonin content of the mid-brain and might thus be important in the pathogenesis of migraine (see section 1.7). The finding of small pupils in the migrainous would be compatible with a physiological defense against such a drop in pineal melatonin by excluding more light than do normal controls.

It is suggested that further studies of the VEP in migraine should be well controlled, including age and sex matching of control subjects, and that the finding by Richey et al (1966) of smaller pupil-size in migrainous should be re-examined with a view to verification.

Thus from the literature one can predict that in response to various rates of IPS a small proportion of the migrainous will exhibit a PCR; that a substantial proportion (between 25 and 95 per cent) will show

an extended photic driving response; the VEP findings support an extension of photic driving in the beta range but show no consistent changes in the individual components at low flash rates.

SECTION 2

METHODS AND THE ANALYSIS OF RESULTS

## 2.1 The development and use of the three questionnaires

For the purposes of this study, the three questionnaires were termed as follows; Headache Questionnaire 1 (HQ1), Headache Questionnaire 2 (HQ2), and Flicker Questionnaire (FQ). They were used for different purposes but the questionnaires had some deliberate overlap to enable cross-checks to be carried out on some information. Copies of the questionnaires are contained in Appendix 3.

### 2.1.1 Headache Questionnaire 1 (HQ1)

Clinical subjects for the study came from the Birmingham Migraine Clinic (see section 2.2) and an age and sex matched non-migrainous control group was required. At the Neuropsychology Unit volunteer control subjects are usually obtained through some form of advertising and this study was no exception (see section 2.2). There was a need for this control population to be screened by some method that would select out migrainous subjects. This method was required to be not only a reliable and valid tool for the research purpose of selection, but also inexpensive, not too time-consuming and acceptable to the subjects.

In addition, it was hoped to parallel the experimental procedures used for the clinical group and their controls with a group of migrainous and non-migrainous undergraduate students. In their case a postal questionnaire with an explanatory letter would be the method to both satisfy University questionnaire regulations and be likely to yield sufficient subjects (see section 2.2).

A preliminary survey of the literature revealed the epidemiological work carried out by Prof. Waters (discussed in section 1.5), which included the development of a questionnaire on headaches. This questionnaire was used in this study with Prof. Waters' permission and is referred to here as HQ1 (see Appendix 2). For this study the questionnaire had the dual advantages of being developed as a postal questionnaire and of being clinically validated (Waters, 1970a; Waters and O'Connor, 1970).

Most definitions of migraine (see sections 1.2 and 1.5) seem to regard the symptoms of unilaterality, an aura (preceeding 'warning' of an attack, notably neurological disturbance, especially of sight) and nausea or vomiting to be of prime diagnostic importance and questions 10, 11, 12 and 14 of HQ1 are specifically related to these three features. However, Waters (1970a) states

"there is no general agreement as to whether one, two or all three of the above features must be present to establish diagnosis."

The results of the clinical validation indicated that in the subjects whose questionnaire showed all three features there was a very high (nearly 90 per cent) correlation with the diagnosis of migraine made by the clinicians in clinical interview. Unfortunately, as regards the ease of selecting subjects for this study, rather less than one third of all migraine sufferers (on a clinical diagnosis) are in the group recording all three features (Waters, 1975c). The majority of the migrainous have only one or two features, and unfortunately quite a few people who are not regarded as having clinical migraine also report one or two features of migraine. The proportion of migrainous to non-migrainous differs according to the combination of features (Waters and O'Connor, 1970, 1971) and the details of this are given in Table 2.1 which is included in section 2.2.

A warning or aura before the headache emerged as the best feature to diagnose migraine with 74 per cent of those reporting a warning being diagnosed by the clinician as migrainous. The correlations between the symptoms reported on these questions and the likelihood of diagnosis of migraine were borne in mind when selecting subjects (see section 2.2).

As one of the criteria for migraine on HQ1 is the presence of a warning or aura, particular note was made of migraine aura in the literature review and the reader is therefore referred to section 1.4 for details of such warning symptoms.

In addition to being a means of preliminary selection between those likely to be migrainous and the non-migrainous, HQ1 also provided a means of checking other salient features of clinical history (see section 2.2) but it was not intended to be used for detailed analysis of the responses, only as a preliminary selection tool.

#### 2.1.2 Headache Questionnaire 2 (HQ2)

An example of this questionnaire is included in Appendix 2. This questionnaire was modified from that used in a preliminary study (Debney, 1973) on the basis of the literature review (section 1.2, 1.3, 1.4 and 1.5) and was intended to serve a number of purposes:

- (a) A secondary screening, following pre-selection by HQ1, of the students and the volunteer controls for the clinic patients (i.e. the clinic control or CC group) for the presence of migraine or non-migrainous headache (NMH).

- (b) A means of screening for any complicating factors
- (c) to obtain information directly relevant to the electrophysiological recordings
- (d) to obtain information on what factors could trigger their headaches (migraine or NMH as appropriate to the group).

Considering the first two of these purposes, the questions in HQ2 which served to cross-check or to supplement information from HQ1 included those on childhood vomiting, travel sickness, skin trouble, epilepsy and head injury (question 1.2, i.e. section 1, question 2 of HQ2) as well as questions on general health, particular symptoms and some therapies (questions 1.3, 1.4, 2.2, 2.4 and 2.5). The information thus obtained was used as follows:-

1. HQ1 had originally been designed by Prof. Waters for epidemiological purposes and not as a selection tool for subjects. As HQ1 asked about headaches in the past year only, subjects were asked whether they had ever suffered any of the symptoms listed. While no-one is expected to have a perfect memory, this did enable the identification not only of some subjects who suffered migraine variants, but also those who while not suffering headaches with migraine symptoms in the last year, had done so previously, and in whom one must assume underlying pathogenic factors could still be present. This supplementary information was important in obtaining control subjects who were most likely not to be subject to migraine, bearing in mind the comments made in section 2.1.1 on the association of symptoms with the likelihood of diagnosis as migrainous.

2. Because of this aim of having as control subjects those least likely to have migraine, if there were a choice between two equally suitable control subjects as regards age and sex-matching to a migrainous subject and their headache symptoms then factors of childhood vomiting, travel-sickness and family history were examined in an effort to use the control subject that was most likely to be non-migrainous. The definition and description of migraine and possible associated disorders were discussed in sections 1.2, 1.3, 1.4 and 1.5.
3. There was a need to identify those people with certain factors that would complicate the experimental procedures or results. Information on head injury was important as it was intended to exclude from further study those people who had experienced a head injury that might have resulted in electroencephalographic (EEG) changes associated with brain damage, as well as those who may have developed symptomatic epilepsy or symptomatic headaches since these features confuse the issues under investigation.

A personal history of coronary thrombosis, especially if recent, was also taken as grounds for excluding the individual, since there could be overlap, and thus confusion, between the symptoms associated with this condition and the symptoms of interest to this study.

A personal history and a family history of epilepsy was requested for two reasons. Firstly, because of the interest in the possibility of a relationship between migraine and epilepsy. Secondly, because it was intended to exclude from the student groups and from the CC group, all those with a history of epilepsy. None of the patients from the



Migraine Clinic, who volunteered to take part in the electrophysiological recordings had a history of epilepsy.

Considering now the third purpose of HQ2, that is the information directly relevant to the electrophysiological recordings, some of these have been mentioned above, that is the need to eliminate complicating factors. In addition a number of factors are known to affect EEG recordings (see section 1.8) and some checks were made using HQ2 with the aim of streamlining the initial part of the electrophysiological recording when such information is usually obtained that is:

- (a) the dominance of the subject (question 1.1)
- (b) information on drugs (question 2.5, 3.4 and 3.5).

At the EEG recording subjects were asked what drugs they had taken in the preceeding 10 days, but it had previously been noted some subjects had difficulty recalling the names of their drugs and these questions, when filled in beforehand, acted as a memory aid.

- (c) information on the menstrual cycle (question 3.2).

As discussed in the literature review a woman's menstrual cycle can affect her EEG recordings. It was therefore helpful to know if an older woman was menopausal, and what was the usual length of a woman's menstrual cycle, so that a reasonable assessment could be made of the stage of the menstrual cycle at the time of recording, from the date of the commencement of a woman's last menstrual period prior to that recording. Incidentally, an additional study on menstrual migraine had been contemplated

originally, which explains the additional detail of Section 3, but in view of the commitments required by the study detailed here, it never materialised.

A fourth major purpose of HQ2 was to collect information on the factors that individuals believed precipitated or "brought on" their headaches. The list given in question 2.3 was put together from those factors which were implicated by various authors, as discussed in the literature review. This information was intended to be analysed to provide group data, unlike the remainder of HQ2 which was intended to aid appropriate selection of subjects and provide information relevant to the EEG recordings.

#### 2.1.3 Flicker Questionnaire (FQ)

The Flicker Questionnaire (FQ), although it is called a questionnaire, is really a set of questions to be used as the basis of a structured interview. This interview was intended to

- (a) ensure the patients from the Migraine Clinic who co-operated in the electrophysiological recordings were those who genuinely thought that visual stimuli, especially environmental flicker, could induce a migraine attack in them (i.e. they had visually induced migraine or VIM). This cautionary step arose from the knowledge that there is a tendency for neurotic individuals to answer positively to any medical question (Waters, 1973b) and that the patients, in what was effectively a preliminary selection, would be asked by their consultant whether glare and flicker precipitated their attacks. In the event, of the 61

patients interviewed only 2 were discarded on these grounds.

- (b) using FQ as a basis to find out from VIM patients which visual stimuli they felt could precipitate a migraine, and which, while not inducing migraine, were particularly distressing. It was intended to compare this information, firstly, with the matched control group, and the student groups with regard to the induction of NMH, and secondly with reports in the literature on precipitants of PSE (see section 2.5).

Two aspects of the FQ need to be considered, its development and its use. When developing the FQ the initial information came from three sources, that is the preliminary study, the review of the literature on migraine and the review of the literature on PSE. During the preliminary study (Debney, 1973) the patient group was asked what factors precipitated their migraine attacks, and although the checklist included bright light, and flashing light no more exact details were recorded. During the experimental session many of those patients mentioned specific situations they felt precipitated their migraine, and the impression was gained that the main ones were cinema, rooms lit by fluorescent lights (especially faulty ones) and oncoming car headlights at night. A search of the literature available (this was in 1974) also yielded the cinema screen and fluorescent lighting and added the everyday situation of television viewing as well as some less common situations including stroboscopes, working with microscopes, travelling past railings, sun reflections from snow, etc.; these and other situations, including those from subsequent literature

are discussed in section 1.6.10 (see Tables 1.6 and 1.7).

An examination of some publications on PSE and a discussion with Prof. Harding on the findings from a considerable number of patients studied (Jeavons and Harding, 1975), revealed that television was a major precipitant of PSE and that the cinema screen, situations producing flickering sunlight, flickering artificial light (including fluorescent lighting and stroboscopes) and certain patterns had also precipitated fits (section 1.9.9). Of these patterns vertical lines were more effective than horizontal ones and Jeavons et al (1972) had found a fine grid to be the most effective pattern for potentiating the effect of flickering light on a photosensitive epileptic. Finally, red light was thought a more effective precipitant of PSE than other colours by some authors, although it might be more correct to say red light is as effective as white light and blue light less effective (see section 1.9.9).

Thus in order to achieve its purposes it was decided FQ should contain situations most people would have experienced and which might be expected to precipitate VIM, that is cinema viewing, television viewing, day-travel and night-travel by car, and fluorescent lighting. In addition a question on the lighting in vehicular tunnels was added since Birmingham has a number of such tunnels and some migraine patients reported travelling through these as precipitating migraine (Hay, personal communication, 1973) and one PSE patient was made to 'feel funny' (Jeavons and Harding, 1975). Finally, questions on pattern and colour were added with a general question on other glare and flicker precipitants.

While the contents of FQ were thus determined, the actual format (see Appendix 2) was developed over the early interviews. It was during these that some of the volunteer patients spontaneously mentioned certain patterns, and a few certain colours, as migraine precipitants. This was particularly interesting as no literature had then been found implicating patterns as precipitants in migraine, although some was later discovered (see section 1.6.10) and no literature implicating colour as a migraine precipitant has been found. As a result of such spontaneous comments a 'swirl' pattern and dots were added to the straight line patterns given as examples in FQ. A 'concentric star' was also included, this was intended to be reminiscent of the fortification spectra experienced as a visual prodrome by some sufferers, and it was hoped this might provoke comments of interest on the pattern, both as a prodrome and as a precipitant.

Despite the format of the FQ, it should not be assumed that the questions were asked in the form that they appear in the FQ; they were intended as prompts for the interviewer with the information being obtained where possible by indirect questioning. For example, while taking the patient along to the interviewing room some comment would be made about a currently popular film or the films being screened at the cinema close to the Hospital and then the patient would be asked if they had seen the film. This elicited responses from "Oh, yes. I love going to the cinema", from which one assumes that the film does not act as a precipitant; through either yes or no "but I have to make sure I am not sitting near the front because then I get a headache", to "No. I stopped going because it made me ill each time." If the response was the less informative bald yes or no then they would be asked something like "You do not go to the

cinema very often then?" and so on. While getting the subject settled and under the pretext of sorting out papers, the responses were recorded and then the next question would be along the lines of "I usually wait until the films are screened on television, but I don't manage to watch as many as I would like to. Do you manage to watch much?" and again the responses recorded. The context of the conversation would then be changed to the means of transport the patient used to get to the Clinic, they would be asked if they drove and whether they liked driving.

Having got this far the subject would then be told that it was wished to find out what situations involving glare and flicker were a problem to the individual patient and a formal review of the comments to that point made with additional questions where necessary and following the format of FQ. Question number 4 to 7 were then asked, again following the format of FQ. Throughout, any spontaneous comments were recorded.

It was hoped this interview method of obtaining information would result in fewer false positives than simply asking patients to either tick off situations on a list or to answer a simple questionnaire. Furthermore it allowed for flexibility and left room for modifications (e.g. the inclusion of additional patterns). Finally, it enabled some rapport to be established with the patients prior to them being asked to come to the University.

## 2.2      Selection of Subjects - The Methods Used

The subjects who took part in this investigation included patients from the Birmingham Migraine Clinic, referred to as the CM (Clinic-Migraine) group, and their matched controls, referred to as the CC (Clinic-Control) group. The other groups consisted of students, those with migraine (SM group) and their controls (SC group) with NMH, and a few students who up to the date of testing, were headache free (SF group). The methods of selection for these groups are described below with the selection of the three student groups being dealt with together.

The permission of the Ethical Committee of the University, the Students Union, and the Hospital Authorities was obtained for the study.

### 2.2.1      Patient Sample (CM group)

Birmingham is fortunate in having a Migraine Clinic. All the patients attending are referred to the clinic by their general practitioner. The work of this investigation was carried out with the co-operation of a consultant at the Clinic. The patients who co-operated in the electrophysiological recordings were selected from those attending the clinic between 1st January, 1975 and 26th May, 1976. Since the consultant kept a record of responses to certain questions of clinical history that were routinely asked it was possible to analyse this data from 265 women and 80 men who attended during this period. This data includes age of onset of migraine; known history of epilepsy; information on precipitating factors including the response to glare and flicker. This data is analysed and discussed in Section 2.3.

The investigator visited the clinic for one afternoon a week by arrangement so that suitable patients could be interviewed. This interview was occasionally a separate appointment but was usually immediately following consultation as this presented the least inconvenience to the subject. Where possible the investigator was present during the consultations as this enabled some initial rapport to be established with the patient and various details to be noted. The initial screening of the patients was carried out by the consultant and those migraine patients who claimed to have VIM and who were not regarded as having any adverse personality or behaviour problems, including claustrophobia, (as they would be required to remain in a sound-damped, windowless room for the electrophysiological recording) were asked if they would both co-operate by answering some questions to do with glare and flicker, and agree to take part in the study being carried out at the University. In co-operation with the consultant those patients who had suffered a severe head injury were excluded from the electrophysiological study, as were those with a history of stroke (cerebro-vascular accident). In the original study (Debney, 1973) one patient had suffered a retinal thrombosis during a migraine attack which might have been expected to have affected the visual evoked potential recording, and therefore it was decided to also exclude from this study those patients who suffered any noticeable permanent visual loss from whatever cause. Finally it was noted if there were any known history of epilepsy, both because of an interest in any relationship between migraine and epilepsy, and because such volunteers could then receive additional monitoring during the routine provocative techniques of the electrophysiological recordings. In the event, no patient with a history of epilepsy attended for recording.



The above factors were double-checked by means of the preliminary interview and by the questionnaires (HQ1 and HQ2). This preliminary interview of a patient by the investigator was carried out in one of the rooms at the clinic where the conversation could take place quietly. The technique used to obtain the information for the FQ was the semi-structured interview and its use in this context is described in Section 2.1.3. As a result of the information thus obtained two patients were rejected as showing insufficient evidence to substantiate their claim that flicker could precipitate their attacks. This was not unexpected for, as mentioned in Section 2.1.3, patients with a high psychoneurotic score are likely to answer positively to any medical question (Waters, 1973).

Having established the patient's sensitivity using the FQ, it was then explained what would be involved in the electrophysiological recordings, any queries answered and the patients asked if they were willing to come to the University for such tests. Some patients were unable to co-operate as they felt that the excessively long journey that would be involved was prohibitive. The laboratory time at the Neuropsychology Unit set aside for this study was a Friday morning and other patients were reluctant to take time off work, or would have difficulty doing so, and special arrangements were made to make the recording at other times to suit the patient. Apart from those considered unsuitable, and those who said they were unable or unwilling to come, two patients were unable to attend appointments because of protracted illness and three patients did not attend appointments. In total this gave fourteen patients for whom details of visual precipitants alone were obtained. The information from these fourteen is considered along with that of the thirty-six others who completed the additional tests, in Section 2.5.

Once a patient had volunteered for the further tests they were given HQ1 to complete while the investigator prepared a set of documents for them to take away. The documents included a leaflet explaining EEGs (see Appendix 3.1); an instruction sheet telling them to note drugs taken in the ten days prior to the test, to eat before they came, etc. (see Appendix 3.2 for text of sheet and Section 2.6 for the reasons for the instructions); and HQ2 for them to complete at home as far as possible. Originally it had been planned for subjects to complete HQ2 during the further tests but it was found to be impracticable as the patients frequently wished to discuss their symptoms and other aspects of their migraine with the investigator. By asking them to complete as much as possible beforehand and then checking it over with them the appointments at the Neuropsychology Unit could be kept to time without loss of verification of information.

It is worth noting that during the preliminary study (Debney, 1973) when patients were approached by letter and not personally with the opportunity for explanations, answering queries and establishing rapport the attendance rate at the Neuropsychology Unit was only 49% for the forty people for whom appointments were made. During this study, of the sixty people originally interviewed, forty-five people completed the further tests, an apparent attendance rate of 75%, but when the people excluded at the preliminary interview as unsuitable or unwilling are ignored the attendance rate was 90% with two people being prevented from attending by illness and only three simply not turning up. This represents a very much more efficient use of the limited laboratory time available, not only in terms of the attendance rate, but also as regards the exclusion of unsuitable subjects. A further advantage of this preliminary interview was that by establishing

contact and rapport the subject's anxiety could be assumed to be reduced. This assumption is reinforced by statements made by some patients to this effect.

### 2.2.2 Selection of control group (CC group) for the patients

Some studies have been open to criticism because of inadequacies in their control groups. Two factors controlled for in this study were age and sex. Apart from any possible EEG changes with ageing, investigations on the VEP generally suggest the VEP amplitude decreases with age, with the exception of the early PI component which increases. However, the correlation between the VEP amplitude and age is low enough to permit for practical purposes, age to be controlled only within broad bands (Dustman and Beck, 1969), that is within periods of 5 to 10 years for an adult population. In this study the criteria of plus or minus five years was used as a target.

With regard to the sex of the subjects, it is suggested by Bergamini and Bergamasco (1967) and by Perry and Childers (1969) that females give VEPs with larger amplitudes and shorter latencies. While the effect of sex on VEPs and EEGs is far from conclusive, it was decided to control for it.

In addition to controlling for age and sex, there was also the need to exclude from the volunteers any with a history of severe head injury, stroke, permanent visual loss, epilepsy and a history of migrainous headache for reasons explained in section 2.1.

The control sampling strategy adopted was to obtain the subjects as far as possible through the Adult Institutes of Further Education, and

to supplement these from volunteers from other sources. Since the order of presentation for the VEP stimuli was different for each patient the ideal allocation of control subjects for age-matching would have been achieved by waiting until after all the patients had been recorded. This however was impractical since once the patients regularly attending the Clinic at the start of the study had been seen, the presentation of patients with infrequent appointments, and of new patients, was irregular. Therefore once the rate of presentation had dropped significantly and a sufficiently high number of patients (about 35) had been recorded to allow matching to be reasonably efficient, steps were taken to obtain subjects from the Adult Institutes of Further Education.

Advertising folders were prepared (see Appendix 3.3), and two or three of these were sent to the head of each of the Adult Institutes of Further Education with a covering letter (see Appendix 3.3). The majority of heads were co-operative and about sixty replies were eventually received over a period of some months. Unfortunately, some of these were from people who stated they had migraine and hoped they could also help, but since controls were sought they were ineligible. When the age matching was carried out there was also found to be a marked excess of retired persons and a slight shortage in some other age groups. This shortfall was more than met by volunteers from among friends and acquaintances, other University staff or research students and their relatives, and friends or relatives of other volunteers, eight of these being used.

Once the replies from the Adult Institutes started arriving, matching of patients and controls started and was adjusted, where possible, as

more replies were received. In some cases volunteers were initially interviewed by telephone to establish their suitability. A fuller discussion on what does or does not satisfy the criteria for migraine on the basis of the answers to questions in HQ1 is given in the papers by Waters and O'Connor (1970, 1971). The information required for practical purposes in this study is summarized from tables in those papers and given in Table 2.1. If they were unlikely to be migrainous and also had no known history of the complicating factors mentioned above, an appointment would be arranged and a letter sent enclosing HQ1 and HQ2 and giving instructions to them (see Appendix 3.4).

Alternatively, a letter (see Appendix 3.5) was sent to them enclosing HQ1, HQ2 and a choice sheet listing available appointments. Once these were returned they were checked for suitability as regards being likely to be free of migraine and not having any complicating factors. If suitable an appointment was made and a letter sent to the individual giving the appointment and instructions for that appointment (see Appendix 3.6).

A total of fifty-five control subjects completed the electrophysiological recordings but of these, only forty-five were used for analysis with ten records being replaced on one or more of the following grounds:

1. Subject found to have a complicating factor, e.g. recent severe coronary thrombosis; history of severe head injury (though not regarded by the patient as such); inadequate vision.
2. Technical difficulties marred the record and a reappointment could not be made (e.g. one subject who was due to move from the district).

TABLE 2.1

Numbers of women aged 20 to 64 with various patterns of headache and proportion diagnosed as migrainous in clinical interview. The figures are taken from Waters and O'Connor (1970, 1971), and were used in this study as an indication of the likelihood of people in the clinic control or student groups being diagnosed as migrainous.

Pattern of headache	Number of women (from questionnaire)	Proportion with Migraine (per cent) (from clinical interview)
None	624	-
Headache only	854	0.0
Unilateral	413	11.8
With warning	100	50.0
With nausea	251	23.5
Unilateral with warning	92	58.3
Unilateral with nausea	238	31.8
With warning and nausea	162	60.0
Unilateral with warning and nausea	199	87.5
TOTAL	2933	

3. The replacement subject was more likely to be free of migraine and was still within the age limits (i.e. plus or minus five years of age of patient).
4. The replacement subject was more or equally likely to be free of migraine and unlike the other subject was within the age limits.

In the group of forty-five control subjects used for analysis, four subjects were outside the target range of plus or minus five years of the patient they were matched to. Subject 49 being six years younger and subject 50 six years older than their patients and subject 75 being eight years older and subject 77 nine years younger than their patients, all these subjects being women. Because the discrepancies are almost equal in the opposite directions it was assumed any differences due to age in these pairs would cancel each other out and the differences are within the 5-10 year period suggested by Dustman and Beck (1969). For the groups as a whole there was no significant difference in average age (CM group average age = 39.8 years, standard deviation(s) = 10.67; CC group average age = 39.4 years, s = 10.84).

### 2.2.3 Selection of student groups (SM, SC and SF groups)

The experimental procedures for the CM and CC groups were to be repeated using a selection of students in whom the migraine group was not selected with any regard as to whether their attacks were precipitated by visual stimuli, and in whom the severity of migraine was assumed to more closely reflect that in the general population. The aims of this were to investigate whether:

- (a) there were any electrophysiological characteristics of those whose attacks were precipitated by glare and flicker
- (b) there were any electrophysiological characteristics or any characteristics of headache precipitants distinguishing the migrainous from the controls
- (c) there was information suggesting a continuum between migraine and NMI rather than the dichotomy suggested in (b)

Before trying to obtain subjects both the target sample size and the method used to obtain subjects had to be decided. From the statistical analysis standpoint it would clearly be beneficial to have as large a sample as possible. When using Student's t-test it is generally held that as the sample size increases to about twenty the risk of making a type 1 error, i.e. rejecting the null hypothesis when it is true, ceases to be a serious danger. Taking twenty as the target size of both samples (i.e. migrainous and non-migrainous), these would need to be subdivided into male and female subjects. There is good agreement in the literature that in migraine sufferers the ratio of adult women to men is approximately 3:2 (Selby and Lance, 1960; Bille, 1969, 1975a; Dalsgaard-Nielson et al, 1970; Waters, 1975). On this basis each sample should contain 14 women and 7 men.

Considering the process of obtaining subjects there were basically two alternatives, the first being to place advertisements round the University asking for volunteers and the second to approach them directly by letter. In both instances two factors had to be examined. Firstly, the proportion of students that could be expected to meet the criteria for migraine (this being the smaller group in the population)



and, secondly, the chance that they would volunteer as a result of being approached by either method.

When considering the proportion of students meeting the criteria for migraine, the likelihood of being diagnosed migrainous with a given pattern of headache as recorded on HQ1 is important (see Table 2.2). If one is willing to accept for experimental purposes only those where the chance of being diagnosed in clinical interview as migrainous is 50% or higher, then the proportion of the population of women with these patterns of headache is 18.8% although only about two-thirds of these would be diagnosed clinically as migrainous. A small proportion of this discrepancy is attributable to incorrect positive answers, e.g. giving as aura features clinically unacceptable as migrainous (Waters and O'Connor, 1970) and it would be aimed to select out these as far as possible. Therefore if 14 migrainous women students were to be located then at least one hundred would have to be approached and since advertisements have a notoriously low rate of response, this method was rejected. Examining the alternative of a covering letter and HQ1 sent by post to students and assuming a minimum response rate of about 30%, then a sample of 200 women students should yield 14 subjects with a suitable pattern of headache given that 18.8% of women have these patterns.

Having arrived at such a large figure for the women it was decided to calculate whether this would be significantly different from the sample size required to estimate the prevalence of migraine in women undergraduates, and at the same time to calculate the equivalent figure for men undergraduates. Since many of Aston University's third year students spend that year in industry, and because the experiment

**TABLE 2.2** Proportion of women aged 20 to 64 (per cent) with various combinations of symptoms, and the proportion of women with these symptoms likely to be diagnosed as migrainous on clinical interview. These figures are taken or derived from Waters and O'Connor (1970, 1971) and are given in rank order from the most to least likely of the combinations of symptoms to be diagnosed as migrainous.

Pattern of headache	In rank order, proportion with pattern of headache with migraine (per cent) (from clinical interview)	Proportion of all women (per cent) who are likely to be diagnosed migrainous (cumulative percent in brackets)	Proportion of women (per cent) with these features (cumulative per cent in brackets)
Unilateral with warning and nausea	87.5	5.9 ( 5.9)	6.8 ( 6.8)
Warning and nausea	60.0	3.3 ( 9.2)	5.5 (12.3)
Unilateral with warning	58.3	1.8 (11.0)	3.1 (15.4)
With warning	50.0	1.7 (12.7)	3.4 (18.8)
Unilateral with nausea	31.8	2.6 (15.3)	8.1 (26.9)
With nausea	23.5	2.0 (17.3)	8.6 (35.5)
Unilateral	11.8	1.7 (19.0)	14.1 (49.6)
Headache only	0	-	29.1 (78.7)
None	-	-	21.3 (100.0)
TOTAL		19.0	100.0

would require access to the students for two consecutive years in order to both administer the questionnaire, with a reminder letter to defaulters, and to carry out the electrophysiological recording, it was decided to restrict the population for study to first year undergraduates from the 1974 intake.

Permission was obtained to get the necessary figures from the Registry Division and these were made available in November, 1974 and included 79 male and 15 female overseas students. These were excluded as HQ1 had been developed and validated on U.K. residents and it was necessary to draw comparisons with the results from Prof. Waters' studies and this one. Furthermore, with some overseas students, their level of fluency in English would call into question their ability adequately to understand and answer the questionnaire. The figures for the new entry U.K. students are given in Table 2.3.

Since the incidence of migraine varies between male and females and because the proportion of men and women in the sample does not reflect the ratios in the population generally, sampling needs to be on a stratified basis. Assuming simple random sampling within the classes and using the following additional assumption the calculations were made using formulae given by Cochran (1963). The following additional assumptions were made:

- (a) margin of error of the calculation; the estimate was required to be within plus or minus five per cent of the true value
- (b) the acceptable risk that the estimated value would be outside the limits of the set margin of error was set at a probability level of 0.05

TABLE 2.3

Figures for new entry students from the U.K. into Aston University, as on the first week of November, 1974.

Course	Male	Female
Full-time	489	187
Sandwich	402	70
TOTAL	891	257

(c) the estimate of the population values from previous work;

at the time the calculation was carried out a paper by Waters (1974b) had recently appeared giving a prevalence figure of 24 to 29% for women and 15 to 19% for men. Since these higher figures than those previously published would result in a larger sample size, it was decided to use them so as to ensure the sample size would provide an adequate estimate.

Using the finite population correction the calculation yielded the following sample sizes:

sample size for men = 123

sample size for women = 137

It was earlier estimated that in order to obtain sufficient migrainous women subjects for the electrophysiological study, about 200 women would have to be contacted, and this is in excess of that required to obtain an estimate for prevalence in first year women undergraduates. While the sample size required for the men would be smaller it is the experience that they tend to be less amenable to volunteering, that resulted in the decision to send out 200 questionnaires (HQ1) to a random sample of the women and 200 to a random sample of the men.

Before the questionnaires could be sent out, the Senate Minute 69/1082 on the control of questionnaires required that the study be approved of by the Deans' Committee, who also gave advice that permission should be obtained from the Guild of Students and this was received on 30th January, 1975.

The approval allowed the release of the names and departments of the new entry students. Unfortunately, owing to computing difficulties, Registry Division did not have the computer printout available until 6th March. From this list the random sample was then made and the covering letter, HQ1 and slip on EEGs sent out to 201 men and 198 women (the variance from 200 being due to experimenter error).

This first letter brought a response from 113 men and 127 women. Those satisfying the migraine criteria (SM group) and those with no headache (SF group) or NMH only (SC group) who had volunteered for the further tests were contacted using the letter given in Appendix 3.8. Once the students returned in October the non-responders to the first HQ1 letter were sent the reminder letter given in Appendix 3.9 to which 36 men and 38 women responded. A further letter to the men defaulters brought the total of responders to 162 men and 165 women. Suitable volunteers for further study were approached by letter (see Appendix 3.10) and appointments were made where possible.

The analysis of the returned questionnaires and the availability of suitable subjects is discussed in the next chapter.

Briefly, HQ1 was sent to a sample of students via their departments. The sample consisted of 201 men and 198 women and the final return rate was 81% from the men and 83% from the women. Excluding those students not willing to volunteer, 103 men and 103 women with varying patterns of headache remained from which to select subjects. The SM group came from those whose symptoms were most likely to be diagnosed migrainous on clinical interview (see Table 2.2), the SF group had never yet had a headache, and the SC group came from those with NMH

only. Those students who volunteered but had a history of severe head injury or epilepsy as indicated by answers on HQ1 were eliminated from those otherwise suitable for further study.

### 2.3 Analysis of the HQ1 data from the student sample

This questionnaire was used purely as a selection device for the purpose of this study but, as was demonstrated in Section 2.2, the numbers sent out were more than adequate to enable them to be used to investigate the prevalence of the various features of headache in the population studied should the return rate be high enough (at least 80%). The return rate of HQ1 also needed to be sufficiently high to produce enough volunteers for this study.

An examination of the numbers returned, as shown in Table 2.4, indicates that as a result of three requests the return rate from the men was 80.6% and after two requests was 83.3% from the women, giving an overall return rate of 82.0%. This rate of return is not as high as some of those achieved by Prof. Waters in his studies, but is still sufficiently high to make an examination of the prevalence of various features worthwhile. This, however, was not one of the aims of this thesis and will not therefore be attempted here. Some such analyses of HQ1 have been carried out and it is intended to present these for publication elsewhere.

From the numbers given in Table 2.4 one might assume that the returns would provide a more than adequate number of subjects for the study. However, a further breakdown is needed to show not only whether subjects indicated on the tear-off slip returned with HQ1 whether they were willing to co-operate or not, but also the features of their headaches which are important for allocation into the experimental groups. These details are given in Tables 2.5 and 2.6. Given the criterion that the only subjects suitable are those whose combination of headache features



TABLE 2.4

Numbers of completed questionnaires (HQ1) returned by the students at the first, second and third request and overall response rates. The questionnaires were sent to 201 men and 198 women.

Request No.	Men	Women	Total
1	113	127	240
2	36*	38	74
3	13	-	13
TOTAL	162	165	327**
Return Rate (per cent)	80.59	83.33	81.95

\* Two men returned incomplete questionnaires and attempts to contact them by letter to get HQ1 completed were unsuccessful. Therefore, analysis being impossible, these two questionnaires were rejected.

\*\* The total number returned was affected by the number of students who failed their first year, withdrew from the course or transferred to other educational establishments. Those not returning questionnaires, who had left the University, definitely included 12 men and 8 women according to Registry records, and may have included 2 more women.

TABLE 2.5

The number of male student subjects stating they were available as volunteers for the electrophysiological study shown according to their pattern of headache.  
(U - unilateral; W - warning; N - nausea).

Available	No H	H only	U	N	U + N	W*	U + W*	W + N*	U + W + N*	Total
No	13	15	15	4	4	1	4	1	2	59
Yes	12	24	17	5	10	8	7	5	2	90
Not Say	2	4	4	1	1	0	0	1	0	13
Total	27	43	36	10	15	9	11	7	4	162

\* These combinations of features had a probability of 50% or more of the individual being diagnosed migrainous (see Table 2.1). If this is used as the cut-off and the "Yes" and "Not Say" categories combined this yields 23 migrainous male volunteers.

TABLE 2.6

The number of female student subjects stating they were available as volunteers for the electrophysiological study shown according to their pattern of headache.  
(U - unilateral; W - warning; N - nausea).

Available	No H	H only	U	N	U + N	W*	U + W*	W + N*	U + W + N*	Total
No	1	17	13	5	3	1	4	1	7	52
Yes	6	26	32	7	23	1	1	2	9	107
Not Reply	2	3	1	0	0	0	0	0	0	6
Total	9	46	46	12	26	2	5	3	16	165

\* These combinations of features had a probability of 50% or more of the individual being diagnosed migrainous (see Table 2.1). If this is used as the cut-off and the "Yes" and "No Reply" categories combined this yields 13 migrainous female volunteers.

has a probability of at least 50% of being diagnosed migrainous on clinical interview (Waters and O'Connor, 1970, 1971), then 25 men and 13 women volunteers are available. These figures would yield enough men for the flicker study but would be one woman short. At the time the sample size was set, the only study envisaged was the flicker study but with the subsequent interest in pattern it was hoped to record two more samples of students, with again 14 women and 7 men in both the SM and the SC group and while this cut-off yields enough men, the number of women is woefully short. Moving the cut-off to include the U + N group with a probability of diagnosis as migrainous as 51.8% yields 54 men and 36 women which is apparently sufficient to provide the required 14 men and 28 women. However we have not yet excluded those with a history of epilepsy or severe head injury.

One female student with unilateral headaches was the only student returning HQ1 who acknowledged a history of epilepsy. Those recording a history of severe head injury were considerably greater in numbers totalling 23 men, 15 of whom were unconscious as a result of the injury and 10 women, of whom 7 were unconscious as a result of the injury. Tables 2.7 and 2.8 show the amended figures. The figures reveal that using the "50% probability of diagnosis" cut-off yields 20 men and 13 women, and if the "U + N" category is also included then 30 men and 33 women are available for the SM group.

Regrettably a high proportion, 38%, of the students who had said they would volunteer failed to reply to letters asking them to co-operate and make an appointment. Of those that did reply a small number were now unwilling to come or unable to do so because of sandwich course commitments outside the University, and a few more did not attend

TABLE 2.7

The number of male student volunteers remaining after those with a history of severe head injury are eliminated. No male students reported a history epilepsy. The students are shown according to their pattern of headache. (U - unilateral; W - warning; N - nausea), and with the probability (per cent) of the combination of features being diagnosed migrainous.

Features	No H	H only	U	N	U + N	W	U + W	W + N	U + W + N	Total of Available Students
Diagnostic Probability	-	0	11.8	23.5	31.8	50.0	58.3	60.0	87.5	
No. Volunteer	11	21	14	5	9	7	6	4	2	79
No. Not Say	1	3	4	1	1	0	0	1	0	11
Total	12	24	18	6	10	7	6	5	2	90

**TABLE 2.8** The number of female student volunteers remaining after those with a history of epilepsy or severe head injury are eliminated. They are shown according to their pattern of headache (U - unilateral; W - warning; N - nausea) and with the probability (per cent) of the combination of features being diagnosed migrainous.

Features	No II	II only	U	N	U + N	W	U + W	W + N	U + W + N	Total of Available Students
Diagnostic Probability	-	0	11.8	23.5	31.8	50.0	58.3	60.0	87.5	
No. Volunteer	6	24	32	7	20	1	1	2	9	102
No. Not Say	2	3	1	0	0	0	0	0	0	6
Total	8	27	33	7	20	1	1	2	9	108

appointments made for them. Ultimately this resulted in only 53% of those contacted actually co-operating. The consequence of this was that 15 of the SM group recorded for this glare and flicker study were asked to return to assist in the pattern study and a similar number of the SC group were also asked back again to balance the pattern study for pre-treatment of subjects.

#### 2.4 Patients attending the Migraine Clinic, data from their records

With the permission of the consultant concerned at the Migraine Clinic, data was obtained from record cards maintained on 264 women and 80 men who attended that consultant during the study period and from whom the CM group was selected. The record cards had a set format and included data on precipitating and aggravating factors, age at first migraine attack, and history of epilepsy. This data was used

- (a) to make a brief comparison of the study data with that in the literature review to check for any obvious disparities
- (b) to compare those patients with visually induced migraine (VIM) with those not affected by visual precipitant factors, with regard to the effect of other groups of precipitant factors
- (c) to estimate whether a history of epilepsy appeared more often than would be expected by chance
- (d) to compare the age of onset of VIM with that of the other patients and with the age of onset of PSE.

##### 2.4.1 Precipitant factors

It is acknowledged that these figures are open to error on several counts. Firstly information obtained from medical records intended for clinical purposes rather than for research has drawbacks as mentioned in Section 1.5, for example, when reporting recognized precipitants verbally patients may only report the major factors which they have considered. Secondly, information obtained retrospectively is open to errors of recall. Thirdly, patients may not



initially recognise the precipitant factors associated with various situations. It can be assumed that errors of recall and recognition would come to light eventually under the guidance of a doctor, particularly if, as at the Clinic, a Migraine Chart is used to record attacks and associated information (Dalton (1973) describes a type of chart), but this 'bringing to light' will take time and will therefore not apply to new patients. Finally, Waters (1973b) remarked on the tendency for neurotic individuals to answer positively to any medical questions. How much these various errors affect the data here or affected the data covered in the literature review (see section 1.6 and Table 1.2) is unclear. Certainly the majority of figures in Table 1.2 came from patient groups, the exceptions being those of Bille (1962) and Henryk-Gutt and Rees (1973), and might be expected to be comparable to those for the patients in this study given in Table 2.9. Moreover, it is known that Hay (1973) used a checklist, and Henryk-Gutt and Rees (1973) used a specially devised item sheet, both of which should reduce the first type of error noted above for those items included on their lists. It was decided as a preliminary step to make a brief comparison of the study data with that in the literature review to check for any obvious disparities. The study data is presented in Table 2.9 and graphically in Fig. 2.1. The data has been grouped in some of the categories as follows:

- (a) psychological stress (emotional or mental stress  
and weekends)
- (b) visual factors (glare, flicker and colour)
- (c) other sensory and environmental (weather and  
temperature changes, stuffy atmosphere, travel,  
noise, fumes and odours).

TABLE 2.9

Precipitating factors affecting the 80 men and 264 women attending the Migraine Clinic during the study period, as recorded in medical notes, and expressed as a percentage of the appropriate sex. (M - men; F- female; T - total). Figures are given to the nearest whole percentage. Some categories are given as an overall figure, e.g. visual stimuli with figures for sub-groups within that overall figure being given below. The categories are given in the same order as those of Table 1.2 for easy comparison. Where a category in Table 1.2 does not appear here it is because no suitable figure were available.

\* These figures of those recognising emotional or mental stress as a precipitant need to be considered alongside additional figures. Those patients with 'worries' noted were 13% of men; 23% of women; 21% of total. Patients noted as markedly tense comprised 56% of men; 71% of women; 67% of total.

\*\* One woman was affected by the colour red and both glare and flicker, one man and one woman were affected by the colour red but not glare or flicker and one woman claimed colour affected her since colour TV precipitated attacks but not black and white TV.

(For body of table, see following page)

TABLE 2.9 CONT'D.

Trigger Factor	M	F	T
PSYCHOLOGICAL			
Emotional or mental stress*	9	24	21
Weekends	10	15	14
PHYSIOLOGICAL			
Physical stress	5	3	3
Lack of food	6	6	6
Oral Contraceptives		14	
EXTERNAL			
Certain foods	40	56	52
Fat	20	32	29
Cheese	15	19	18
Chocolate	18	27	25
Other	24	33	31
Alcohol	18	24	22
Climate (Heat or Cold)	-	2	1
Stuffy Atmosphere	-	3	2
Travel	4	8	7
Tobacco Smoke	-	2	1
Fumes and Odours	1	3	2
Noise	6	6	6
Visual stimuli	58	67	65
Glare	56	64	62
Flicker	44	56	53
Colour**	1	1	1

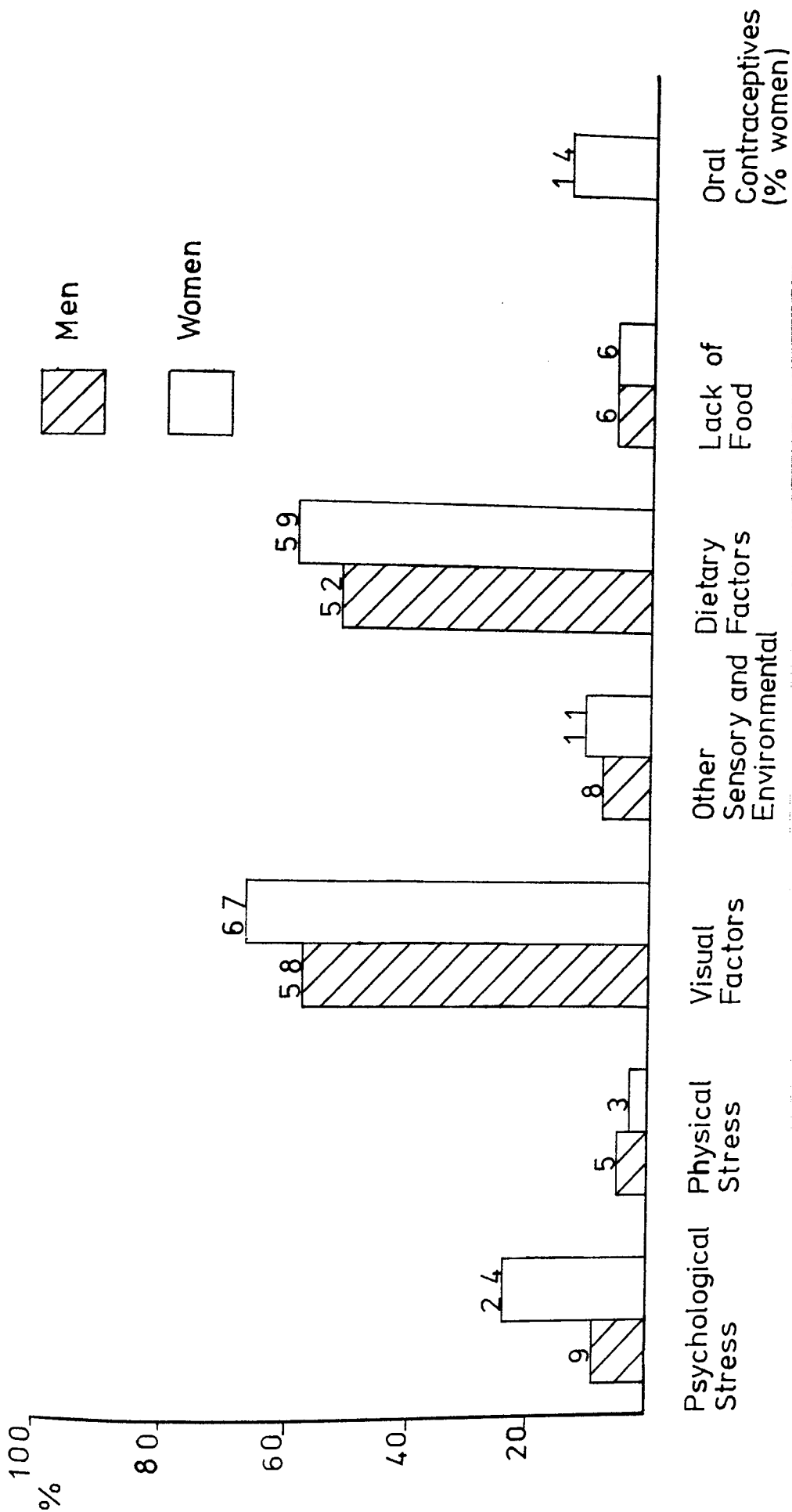


FIG. 2.1 Precipitating factors affecting the 80 men and 264 women attending the Migraine Clinic during the study period, as recorded in medical notes, and expressed as a percentage of the appropriate sea (i.e. 264 women = 100%; 80 men = 100%). See also Table 2.9 and Text (section 2.4.1).

(d) dietary (foods and alcohol)

The figures from Table 2.9 show a stuffy atmosphere (mentioned in section 1.8.2 in connection with ionization of the atmosphere), climate (heat or cold), smells and odours, noise and tobacco smoke all to be minor precipitants, which is as noted on Table 1.2.

Unfortunately it is unclear whether those affected by tobacco smoke are affected by a relatively small quantity or only if it is a smokey atmosphere and factors associated with a stuffy atmosphere might come into play. However, none of those affected by tobacco smoke also mentioned a stuffy atmosphere and only one of the four affected mentioned an odour, in this case 'perfume'. With such a small number in this sub-group no firm conclusions can be drawn.

The category 'lack of food' showed a wide variation in figures in Table 1.2 and those found here around 6% fit between the lower pair of Arthur (1974) and Pearce (1976) who found 4% and 7% respectively. A number of other factors are, however, under-represented as compared with Table 1.2, these including physical stress, travel, the weekend, and emotional or mental stress. It is unclear whether these are true differences, reflect differences in life-styles or reflect the sources of error previously mentioned. Examining the figures for those recognising emotional or mental stress, these can be seen to fall greatly short of those given in Table 1.2 but this could be due to lack of recognition by the patient rather than to lack of occurrence. This suggestion is supported in that many of those noted as worrying were not noted as recognising psychological factors as precipitants. Moreover about 80% of those with worries were also markedly tense. While the figures for the markedly tense are close to those for

emotional or mental stress given by Selby and Lance (1960) and Pearce (1976), they cannot be equated, since the source of the tension is not necessarily known, it might, for example, be as a result of sympathetic over-activity from one of a number of causes (as discussed in Section 1), including, possibly, the combined emotional and travel stresses involved in visiting the Clinic in the city centre.

The figures for female hormonal factors in Table 1.2 refer to general hormonal factors and not to oral contraceptives specifically as here. Blau (1970) reported migraine as being exacerbated by the oral contraceptives in about 10% of women. Henryk-Gutt and Rees (1975) also found 10% of their classic and common migraine groups of women had "headaches and/or depression" caused by oral contraceptives. The slightly higher figure here might reflect nothing more than a greater number of women using oral contraceptives; in this group 46% of the women have used or were using them. What does not emerge from Henryk-Gutt and Rees, but is mentioned by Blau (1970) is that some women have their attacks lessened, and he suggested this was "a smaller proportion". The medical records for the group here suggest 38% reported a lessening of migraine. To put these in perspective, of those reporting the effects of oral contraceptives 83% found their migraine improved and 31% had attacks worsened but 17% reported both improvement and worsening, presumably to different types of oral contraceptive with different proportions of hormones, so that only 14% of women reported the only effect was to worsen migraine.

The three major precipitants found in this analysis of medical records were alcohol, dietary factors and visual stimuli. The role of alcohol, reported as affecting 18% of men, is similar to that of Henryk-Gutt and

Rees (1973) which is half that of Arthur's (1974) New Zealand study. Conversely the figure of 24% of women affected is closer to that of Arthur's 30% than to Henryk-Gutt and Rees' 10% of their English women civil servants. Thus the final total of 22% lies between that of these two authors but is over double the population figure of 10% reported by Pearce (1976). There is no obvious reason why women should be more affected in this group, in contrast to the other two studies reporting men and women separately.

Four of the five previous studies on adults report 20 to 26% of persons being affected by diet whereas the 52% noted on the medical records is double that. Whether this is a true figure or whether it reflects the high level of publicity given to food triggers in the mass media and individuals 'latching on' to this possible cause for their misery, is a question only further research can answer.

Finally, there are the visual stimuli, since every patient was specifically questioned about glare and flicker in order to check on suitable subjects (apart from one blind woman), the figures should be representative, bearing in mind the sources of error mentioned previously. At a total percentage of 65%, this is higher than that of Selby and Lance (1960) at 47% and Pearce (1976) at 30% but less than that of Bille's (1962) group of children at 84%, the other authors not reporting a single overall figure for visual stimuli. Arthur (1974) separates his figures into three categories of sunlight; glare, shimmering light; and eye strain, films, TV. These are not absolutely parallel factors to the broad categories of glare and flicker used in the medical records but it is clear that a higher proportion of the Clinic patients reported sensitivity to visual stimuli. As Arthur

simply states "inquiry into trigger factors produced the following data" one cannot know if he specifically asked the patients about these factors, if not, his figures might be an understatement. However, both studies indicate that a greater percentage of women are affected, with Arthur noting a larger difference than the present study. One aspect of visual stimuli that was unexpected was the inclusion of colour as a factor with three people independently reporting the colour red as a problem and the fourth stating that colour televisions affected her but not black and white. The last patient, may, of course, not simply be affected by the colour if, for example, colour televisions watched have larger screens or she sits closer to them than is the case with black and white, either way the area of the retina stimulated is increased; she is, however, included since colour is possibly a factor.

In summary, the figures obtained from the medical records do show some variation from and some similarities to those of previous authors and some possible reasons for this have been reported, and because of these no firm conclusion can be reached as to overall similarity or dissimilarity between this study and others. Whatever the sources of variation all, except Henryk-Gutt and Rees (1973) who gave figures for a multifactorial group in a non-patient sample, found visual stimuli to be of significance although the figures from the present study are at the upper end of the range, perhaps because patients were specifically asked. It is relevant to ask whether visual stimuli might be a more potent precipitant in patients, with presumably more severe or persistent migraine, than in the migrainous in general or whether Henryk-Gutt and Rees (1973) did not probe this aspect, being mainly interested in psychological factors. Finally, a small number of people



cited colour, notably red, as a precipitant, a factor not found elsewhere in the literature on migraine.

At this point the question naturally arises, whether patients whose attacks can be precipitated by visual stimuli differ from those whose attacks are not influenced by this factor. Since it is seldom that patients have only one precipitant of their attacks, the medical records were re-examined and divided into those triggered by visual stimuli and those not, and then the two groups examined for incidence of other precipitants, see Fig. 2.2. By inspection two things are immediately obvious:

1. Both groups exhibit a similar rank order of other precipitants. This suggests any difference is one of degree rather than kind.
2. Those sensitive to visual stimuli are more sensitive to other groups of precipitants than are those not affected by visual stimuli. This difference reaches significant proportions (chi-square test) for dietary factors ( $p < 0.001$ ) and other sensory and environmental factors ( $p < 0.05$ ).

Given the assumptions that those triggered by visual stimuli are more easily triggered by all stimuli and that therefore they have a lower threshold to migraine attacks, then a number of queries are raised.

1. Is this because they have a higher level of arousal, whether this be sympathetic arousal of the A.N.S. or hyper-excitability of cortical neurons, and thus are closer to the threshold for attacks?

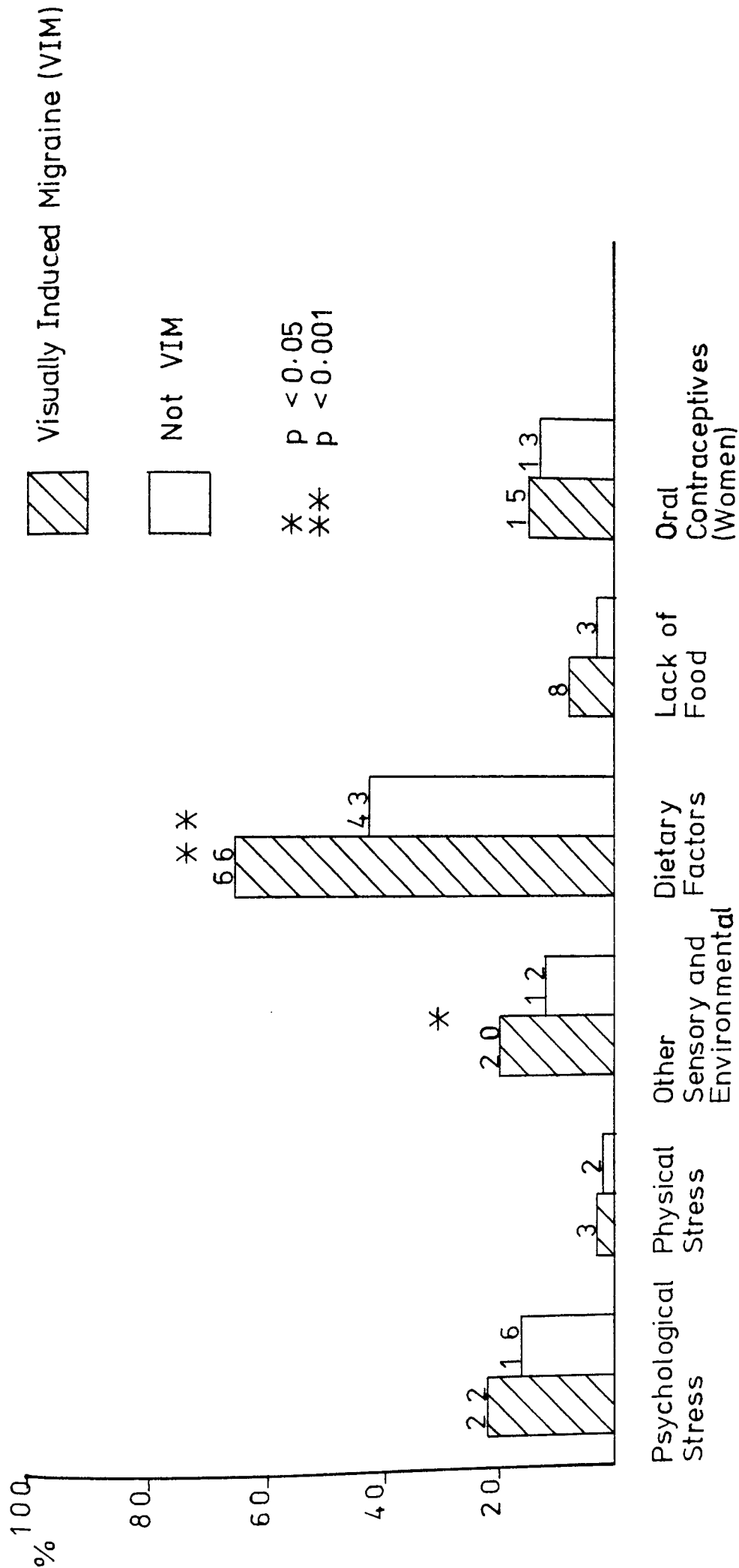


FIG. 2.2 Precipitating factors affecting the 47 men and 178 women with visually triggered migraine, and the 33 men and 86 women not affected by visual stimuli, as recorded in medical notes and expressed as a percentage of the appropriate group. For details of groupings of factors see text (Section 2.4.1).

2. Given that abnormalities of biogenic amines and their metabolism relate to neurological function and have been associated with dietary precipitation of attacks, does the highly significant increase in sensitivity to dietary factors indicate that those affected by visual stimuli show this biochemical abnormality to a greater degree?
3. Following on from the second question, does the degree of biochemical abnormality (e.g. extent of lack of mono-amine oxidase) relate to severity of migraine, and if so, would this contribute to the high level of visual precipitation (84%) found by Bille (1962) in a highly selected group of children with pronounced migraine, the lower levels in patient groups and the small proportion indicated by Henryk-Gutt and Rees (1973) for a group of civil servants with presumably few severe cases?

#### 2.4.2 Data on the incidence of epilepsy and the age of onset of migraine

The literature considering a relationship between migraine and epilepsy was critically considered in section 1.9. That discussion to which the reader is referred, included reasons why one might expect groups of migraine patients to exhibit a higher incidence of epilepsy than the migraine population as a whole. Therefore, the finding that 5 (1.4%) of the patients had a history of epilepsy, as compared to a population incidence of epilepsy of 0.5% does not necessarily indicate any genetic connection. Of the 5 patients (4 women, 1 man), one woman had had infantile spasms and another had had epilepsy in association with a particular illness. No further details were available.

The age of onset of migraine is presented in Figs. 2.3 and 2.4 as grouped data as some patients gave only an approximate indication e.g. 'early teens' or 'late teens', and the data for PSE in Fig. 2.5 is therefore also presented as grouped data to make visual comparison possible. As the three groups are of different sizes, the data is presented graphically as percentages of the appropriate group to enable direct visual comparison to be made. In section 1.5 studies giving details of the distribution of the age of onset of migraine were discussed and both the VIM patients and those not so induced, conform to expectations that the peak age of onset is around the age of puberty and that the condition may not become manifest until relatively late in life. Comparing the two groups from the Migraine Clinic (Figs. 2.3 and 2.4) there is no difference in the age of onset of the two groups as a whole and there is no difference in the age of onset of migraine in the men, but in the women with VIM the age of onset is significantly younger than in the other women ( $p < 0.01$  two-tailed  $t$  test). This difference in the women appears from the graphs to have two contributing components; firstly, more of the VIM women have their first attacks around the ages when menstruation starts, and, secondly, the other women show a sharp rise of onset in the age-group 25 to 30 which might be associated with pregnancy (this is unclear from the records), and these two components combine to give a significant difference. The role of female hormones in migraine was considered in section 1.6, to which the reader is referred.

The distribution of age of onset of PSE given in Fig. 2.5, is derived from the figures given by Jeavons and Harding (1975), who give the modal age as 12 years, the mean age as 13.7 years, and the age range

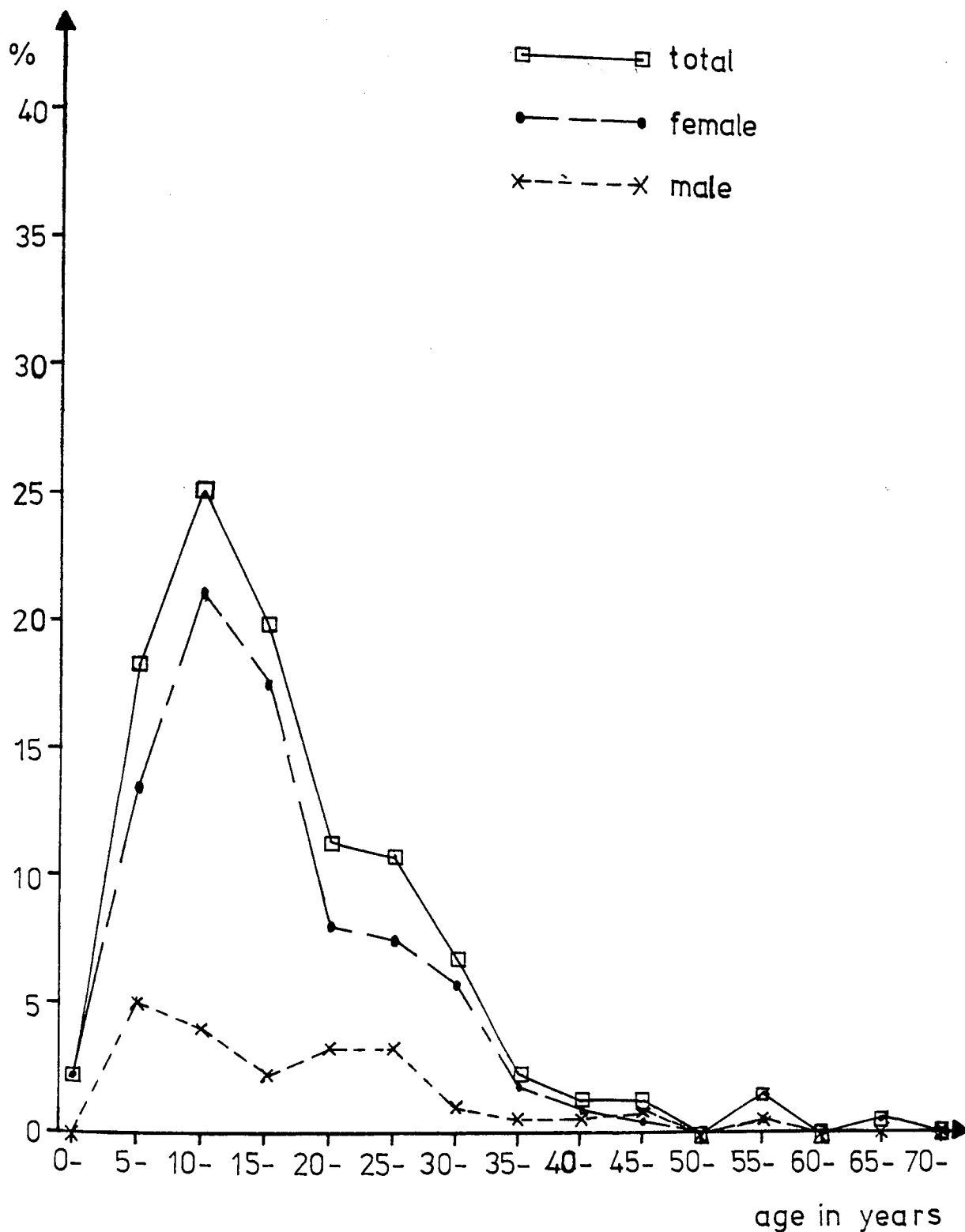


FIG. 2.3 The age of onset of migraine in clinic patients with visually induced migraine (VIM), expressed as a percentage of the group.

(Women  $\bar{x} = 17.53$ ,  $n = 178$ ; Men  $\bar{x} = 18.74$ ,  $n = 47$ ;  
Total  $\bar{x} = 17.98$ ,  $n = 225$ ).

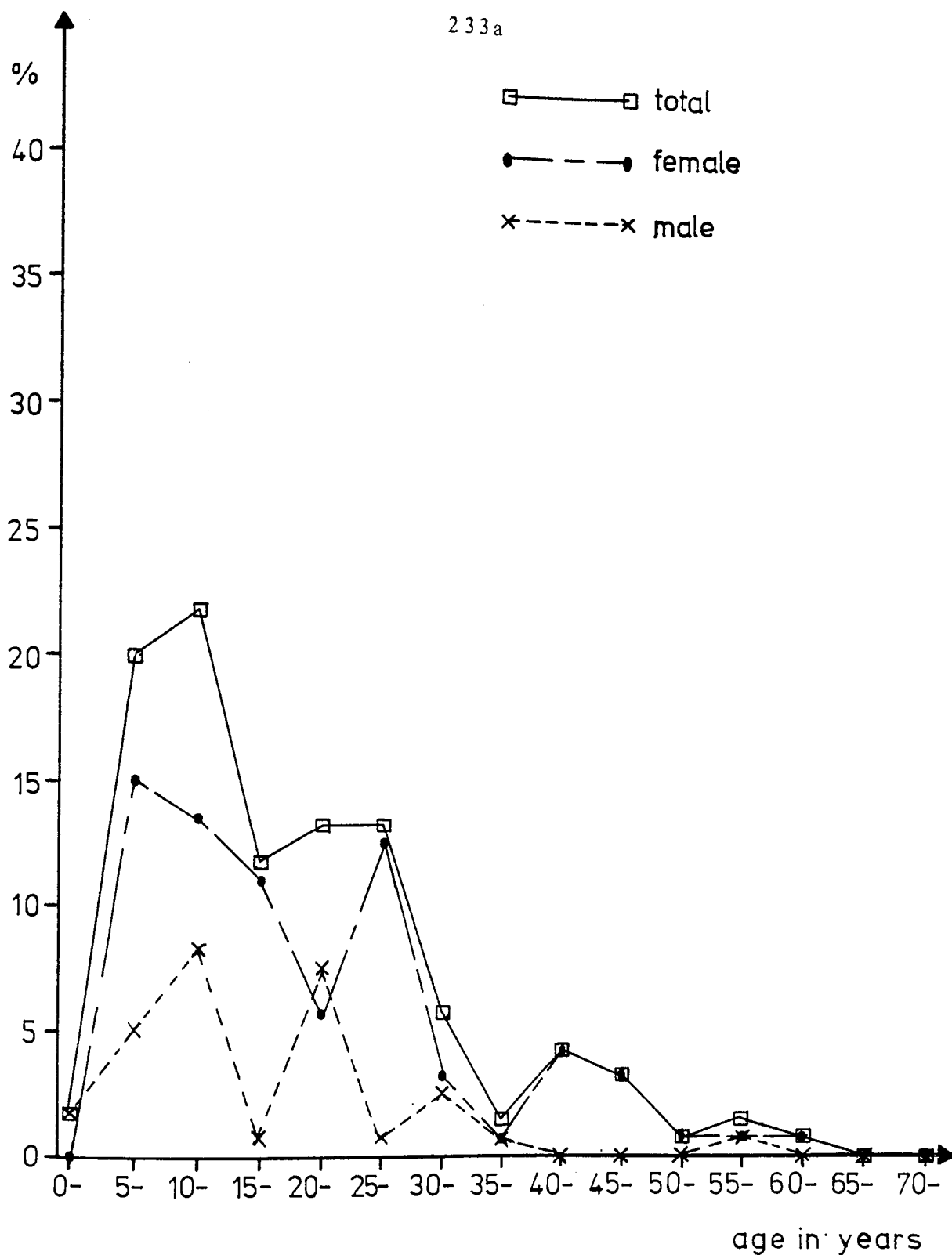
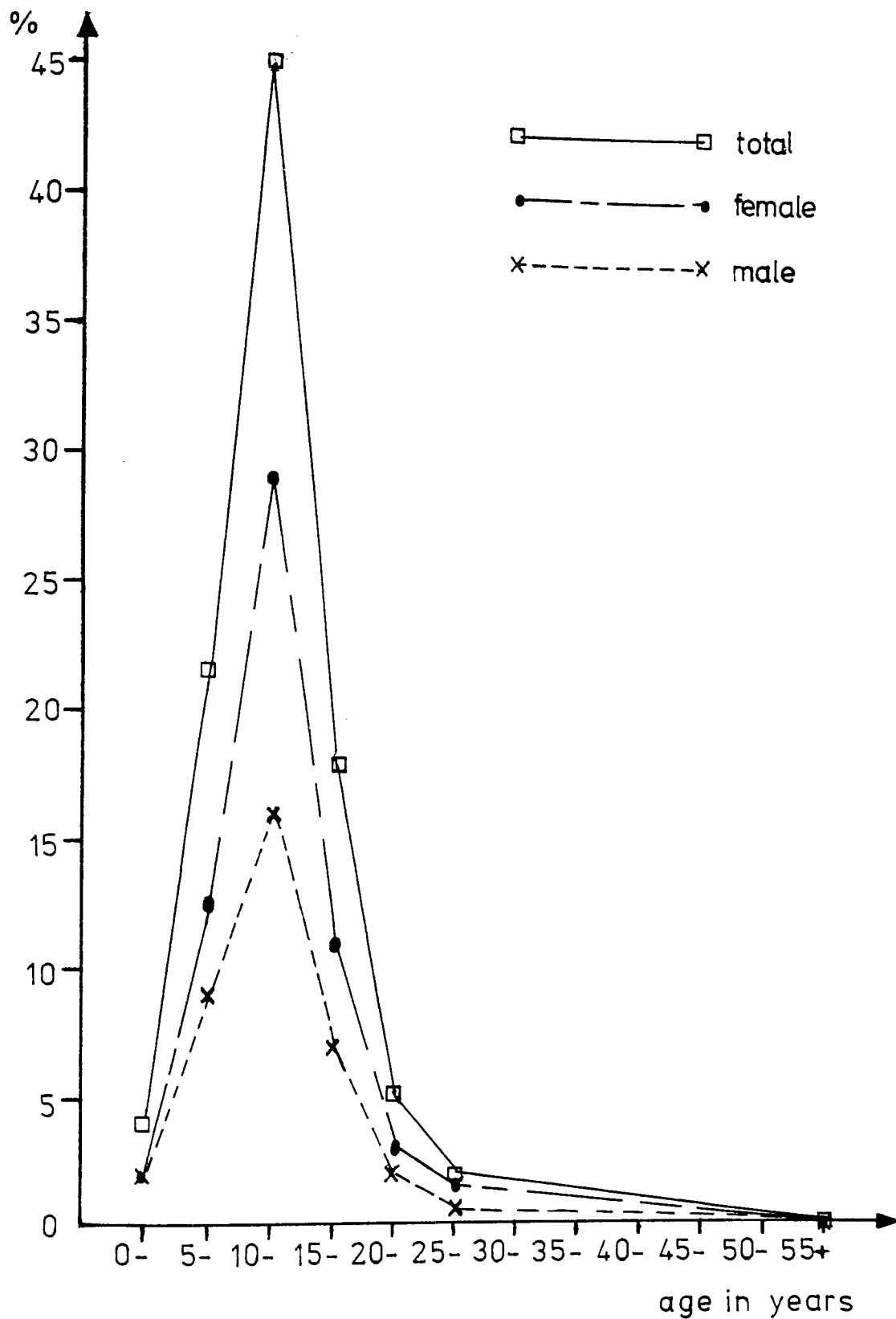


FIG. 2.4 The age of onset of migraine in clinic patients whose attacks are not precipitated by visual stimuli, expressed as a percentage of the group.

(Women  $\bar{x} = 21.30$ ,  $n = 86$ ; Men  $\bar{x} = 17.59$ ,  $n = 33$ ;  
Total  $\bar{x} = 20.25$ ,  $n = 119$ ).



**FIG. 2.5** The age of onset of photosensitive epilepsy. Figures obtained from Jeavons and Harding (1975).  
 Modal age of onset = 12 years, Range 2 to 58 years.  
 (Women  $\bar{x} = 13.0$ ,  $n = 281$ ; Men  $\bar{x} = 14.0$ ,  $n = 173$ ;  
 Total  $\bar{x} = 13.7$ ,  $n = 454$ ).

as 2 to 58 years. As can be seen the distribution is narrow and very few patients, less than 2.5%, have their first attack over the age of 24. In comparison those with VIM, see Fig. 2.3, show a similar peak age of onset (between 10 and 15 years) and a similar range of 3 to 67 years. However, those with VIM show a much wider distribution with a marked positive skew, and have a higher mean age of onset of 18 years. Thus on inspection the distributions appear to be different. Unfortunately the distribution of the VIM patients in Fig. 2.3 does not approximate sufficiently to normal to make the use of the z-test entirely valid. However, the z-test was the most suitable test found for comparing the two groups and indicated the mean age of onset in the visually induced migraine patients to be significantly higher than that of the PSE patients ( $p < 0.001$ , two-tailed test). This suggests the two groups do not come from the same population even though influences, perhaps hormonal, at the age of puberty play a role in precipitating the first identifiable attacks in both conditions.

The role of female hormones in migraine was discussed in section 1.6 and have been suggested as helping to produce the predominance of migraine in women which is generally accepted as yielding a female to male ratio of 3:2 (see section 1.5). The ratio for females to males in the VIM group is 3.3:2 which is close to the population values. According to Jeavons and Harding (1975) photosensitive epileptics also show a female to male ratio of 3:2 and this is at variance to that for the general epileptic population in whom males tend to predominate. A discussion on why females should be more susceptible to PSE is outside the scope of this study but as suggested in section 1.9 a comparison of the biochemical abnormalities known to occur in epilepsy, and in this case PSE, with those discovered in



migraine might more firmly establish why those with PSE and those with flicker induced migraine show certain superficial similarities, and yet are different.

## 2.5 Precipitant (trigger) factors in the study groups

In section 1.6 the literature was analysed to extract a list of migraine precipitants and part of that literature gave figures for the proportions of migraine sufferers or migraine patients affected by certain precipitants. However, it was not the purpose of this study to compare in any detail the results obtained here with those of earlier studies. As mentioned previously the intention was:

- (a) to use the check-list of trigger factors extracted from the literature and included in HQ2 (see section 2.1.2), as a means of checking whether there is a discontinuity between the migrainous and those with non-migrainous headache (NMH) as regards the type of factors which will trigger their migraine or NMH respectively, or whether they appear to lie on a continuum,
- (b) to again check for any dichotomy or possible continuum between the migrainous and those with NMH but using the interview information obtained with FQ on the effects of certain visual stimuli on the individual,
- (c) to use the interview information mentioned in (b) to compare the visual stimuli triggering visually induced migraine (VIM) with those reported in the literature as precipitating PSE.

### 2.5.1 Precipitants in general

All the CM group have migraine triggered by visual stimuli of one type or another since this sensitivity to visual triggers was one of the criteria for their selection. However, this sensitivity was not a requirement for the SM group since their selection, as shown in section 2.2.3, consisted of selection based on the three features of migraine (unilaterality, aura and nausea), substantiated by additional information. Even so, 84 per cent of the SM group reported visual stimuli as a precipitant, a figure identical to that found by Bille (1962) in his pronounced migraine group. In comparison NMH occurred in response to visual stimuli in 47 per cent of the CC group and 37 per cent of the SC group, which while considerably lower is still a substantial proportion.

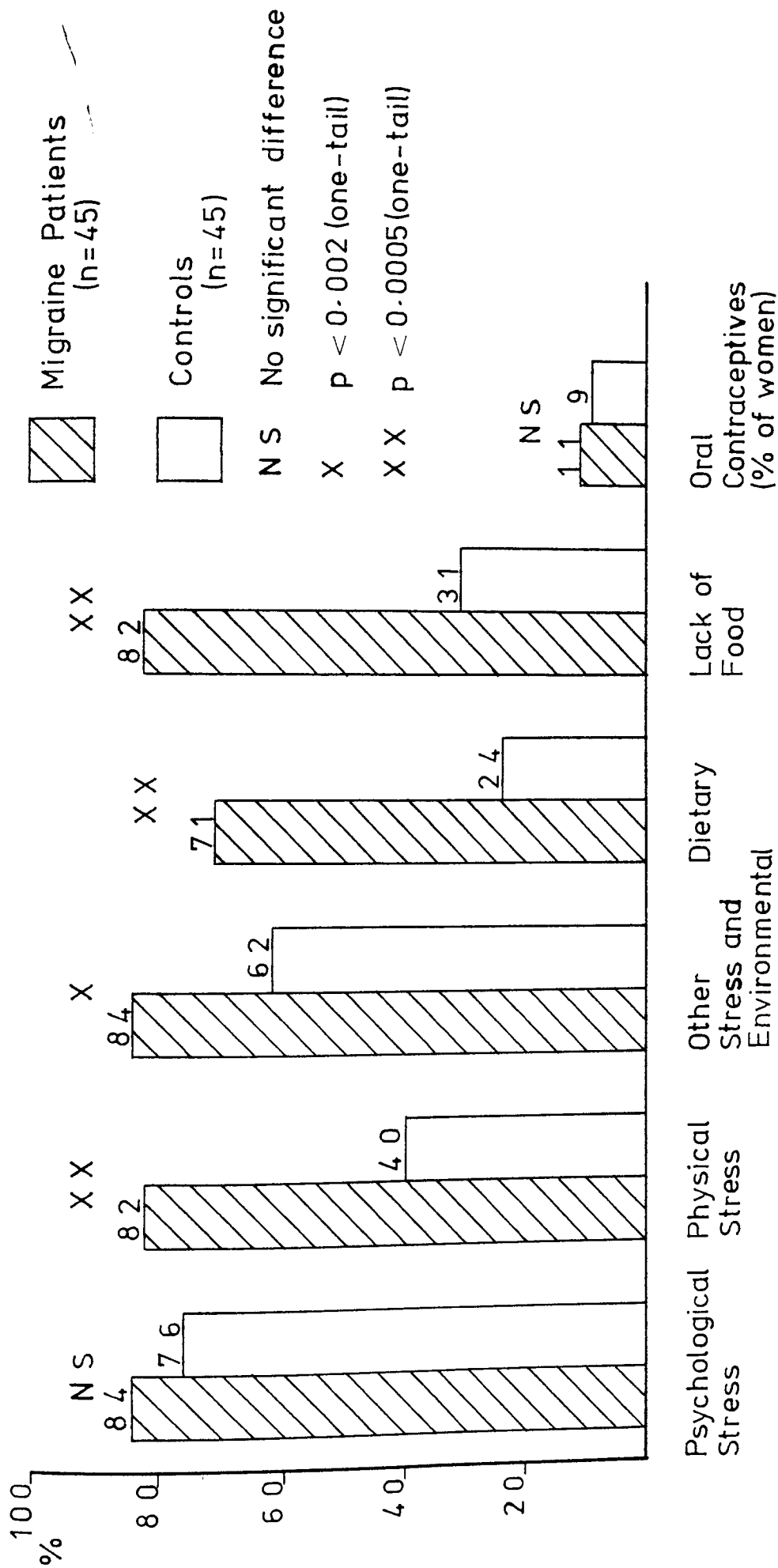
Some students were used in both this study and the study on pattern responses because of the difficulties in obtaining migrainous students as described in Section 2.3. When a migrainous student was used in both studies their matched control was also used in both as far as possible. The final grand totals were 25 migrainous students and 31 control students all of whom completed HQ2. Some of these students came for the electrophysiological recordings in the summer of 1975 before FQ was in final form. Of these, all the migrainous students later co-operated by completing FQ but 6 of the control students did not do so (two of whom are known to have left the University). Thus the data from FQ for the SC group is based on 25 students with NMH.

Some authors have questioned whether migraine is a separate condition as indicated by its associated vascular abnormalities, dietary sensitivities and premenstrual disturbances, or whether it is just

the intense end of the headache spectrum (Waters and Cochrane, 1970; Waters, 1973b, 1975e; Hannington-Kiff, 1974). The data obtained here, using the HQ2 list, on sensitivity to precipitant factors is displayed in Figs. 2.6 and 2.7 and it is immediately apparent that each of the types of trigger affect some of the control subjects and that a larger proportion of the migrainous are affected. In Table 2.10 the rank order of importance of the different groups of factors precipitating migraine or NMH in the study groups is shown and it becomes clear that the factors are in virtually the same rank order. This finding would suggest the presence of a continuum rather than a dichotomy. A closer examination of the exceptions in the rank order reveals:

- (a) in the SM group 'lack of food' ranks higher due to 'other sensory and environmental' and 'physical stress' factors showing a slightly decreased relative potency, although all three precipitants affect a high percentage of the SM groups and their figures are close to those of the CM group, (see Table 2.10).
- (b) 'lack of food' also ranks slightly higher in the SC group and it might be that this elevation of 'lack of food' in the student rankings reflects missed or skimmed meals in student life and thus awareness of this as a factor.

If a continuum were to exist then one would expect the CM group, assumed to have relatively severe migraine, to be more affected by the various triggers than the SM group, who in turn should be more affected than the control groups. It is possible age factors might influence the comparison between the student groups and the other groups, but as there were no significant differences between the CC and SC groups it was assumed this did not unduly influence these



**FIG. 2.6** Precipitating factors affecting the 10 men and 35 women patients selected for the study and their age and sex matched controls, as recorded in HQ2 (Section 2, Question 3) and expressed as a percentage of the appropriate group. For details see text (Section 2.5).

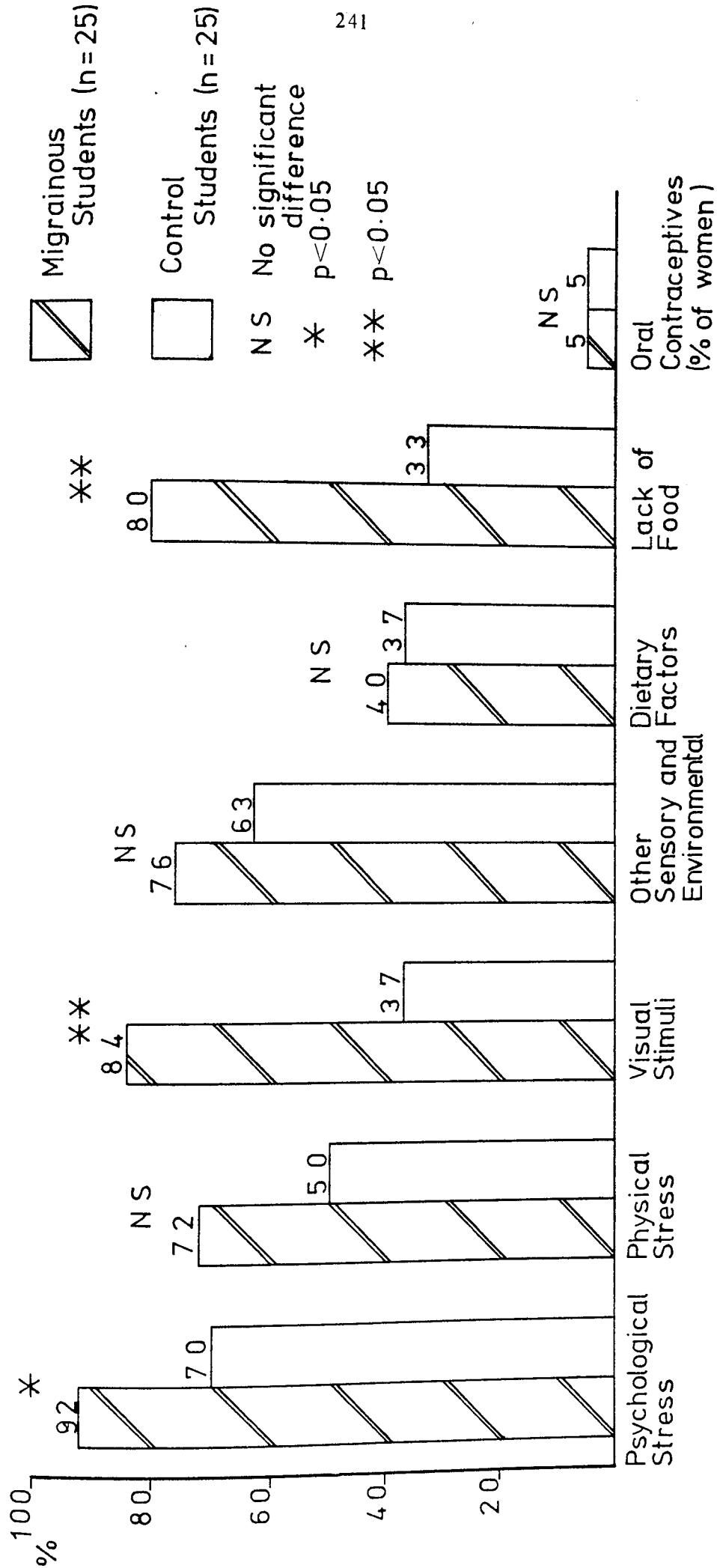


FIG. 2.7 Precipitating factors affecting 18 female and 7 male migrainous students and 21 female and 10 male non-migrainous students, as recorded in HQ2 (Section 2, Question 3) and expressed as a percentage of the appropriate group. For details see text (Section 2.5).

TABLE 2.10 The groups of precipitating factors, other than visual stimuli, shown in rank order for the CM group with the appropriate ranks for the other groups being indicated in addition to the percentages affected in each group.

Precipitating Factor	Groups							
	CM		SM		CC		SC	
	Rank	%	Rank	%	Rank	%	Rank	%
Psychological Stress	1	84	1	92	1	76	1	70
Other Sensory and Environmental	1	84	3	76	2	62	2	63
Physical Stress	3	82	4	72	3	40	3	50
Lack of food	3	82	2	80	4	31	5	33
Dietary factors	5	71	5	40	5	24	4	37
Oral Contraceptive	6	11	6	5	6	9	6	5

findings. A comparison between the CC and CM groups yields no significant differences in the proportions affected by psychological stress or in the proportion of women affected by oral contraceptives, but the other factors show significant, mostly highly significant, differences (see Fig. 2.6). In contrast a comparison of the SM and SC groups while again showing no significant difference in the response of women to oral contraceptives, did show a just significant difference to psychological stress and the same degree of difference to lack of food but all the other differences were now none significant. Since there was no significant difference between the CC and SC groups these findings might indicate a trend towards the postulated continuum from severe migraine to NMH. However, a comparison of the percentages of the subjects affected in the CM and SM groups, while it revealed that, apart from psychological stress, a smaller proportion of the SM group were affected by the different factors, the only factor showing a significant difference was diet ( $\chi^2$  test,  $p < 0.02$ ) with 71 per cent of the CM group affected and 40 per cent of the SM group. In section 2.4 it was shown that migraine patients sensitive to visual stimuli were significantly more affected ( $p < 0.001$ ) by dietary factors than those not so affected, and here is a group in which visual stimuli affect a high percentage, but whose members are presumed to suffer less severe migraine and are also significantly less affected by diet. While part of this discrepancy may be due to lack of recognition of food as a precipitant by students it is still compatible with the possibility suggested in Section 2.4 that the degree of biochemical abnormality associated with dietary sensitivity might relate to the severity of migraine.



Before examining this possibility further it is essential to look more closely at the category of 'dietary factors'. In the CC group all except one of the eleven individuals quoted alcohol as the culprit, the eleventh individual indicating coffee as his dietary factor. By comparison only five of the CM group indicated that unspecified alcohol alone was a factor, whereas three others indicated that only red wine and sherry affected them and the latter amine-rich drinks are recognised migraine precipitants. If one assumes that those citing unspecified alcohol only, suffer resultant hangover headaches (i.e. not migraine or tension headache) and deletes them from the dietary factors group, the significance of the difference between the CM and CC groups shown on Fig. 2.6 is greatly increased from the already highly significant level of  $p < 0.0005$ . If those subjects affected by unspecified alcohol only are similarly deleted from the student groups then four (16 per cent) of the SM group and one (3 per cent) of the SC group are affected by dietary factors. Using these new figures there is not a significant difference ( $p < 0.15$ ) between the SM and SC groups. The one SC subject referred to was affected by "spicy foods". Thus in both control groups true dietary factors, excluding alcoholic hangover, are reduced to insignificant proportions. The final amended figures for the proportion of each group affected by dietary factors are as follows: CM group 60 per cent; SM group 16 per cent; SC group 3 per cent and CC group 2 per cent, which again suggests a continuum from severe migraine to NMH.

The question of a dichotomy or a continuum between the migrainous and those with NMH is discussed in relation to arousal and the underlying mechanisms of migraine in section 3.

Before passing on to visual precipitants a comparison of Figs. 2.2, 2.6 and 2.7 will be made. A considerably lower incidence of factors other than dietary, can be seen to have emerged from the medical records. This is unlikely to be due to a factor in the selection of the CM group, e.g. severity of migraine; as the CM group resembles the SM group more closely than it resembles clinic population responses. It appears more likely that the study groups ticked items on the questionnaire list that had not been recorded on the medical notes, perhaps because patients did not think of them at the time, or because they report only those factors they consider major triggers, or because they will not report items they feel may be regarded as 'silly', e.g. "if one knows lack of food results in headaches, the remedy is obvious" as one patient said. What cannot be obvious is how many false positives, if any, were recorded on the questionnaire. Certainly the general similarities between the figures of the two study migraine groups and between their two control groups, suggests consistency within the migrainous and within those with NMH and it is assumed any false positives did not affect the overall picture.

#### 2.5.2 Visual precipitants

A closer examination of visual precipitants, as recorded using the FQ , reveals not only a graded response to these, hence the form of presentation in Figs. 2.8 and 2.9, but also some comments of relevance. In both the CM and SM groups over half spontaneously distinguished between those factors which can precipitate migraine, those which have caused "ordinary headaches" only (although it is unclear how many of these "ordinary headaches" were tension headaches of a mild, rather than a full-blown, attack of migraine), and those which they found distressing and unpleasant, some feeling "funny",

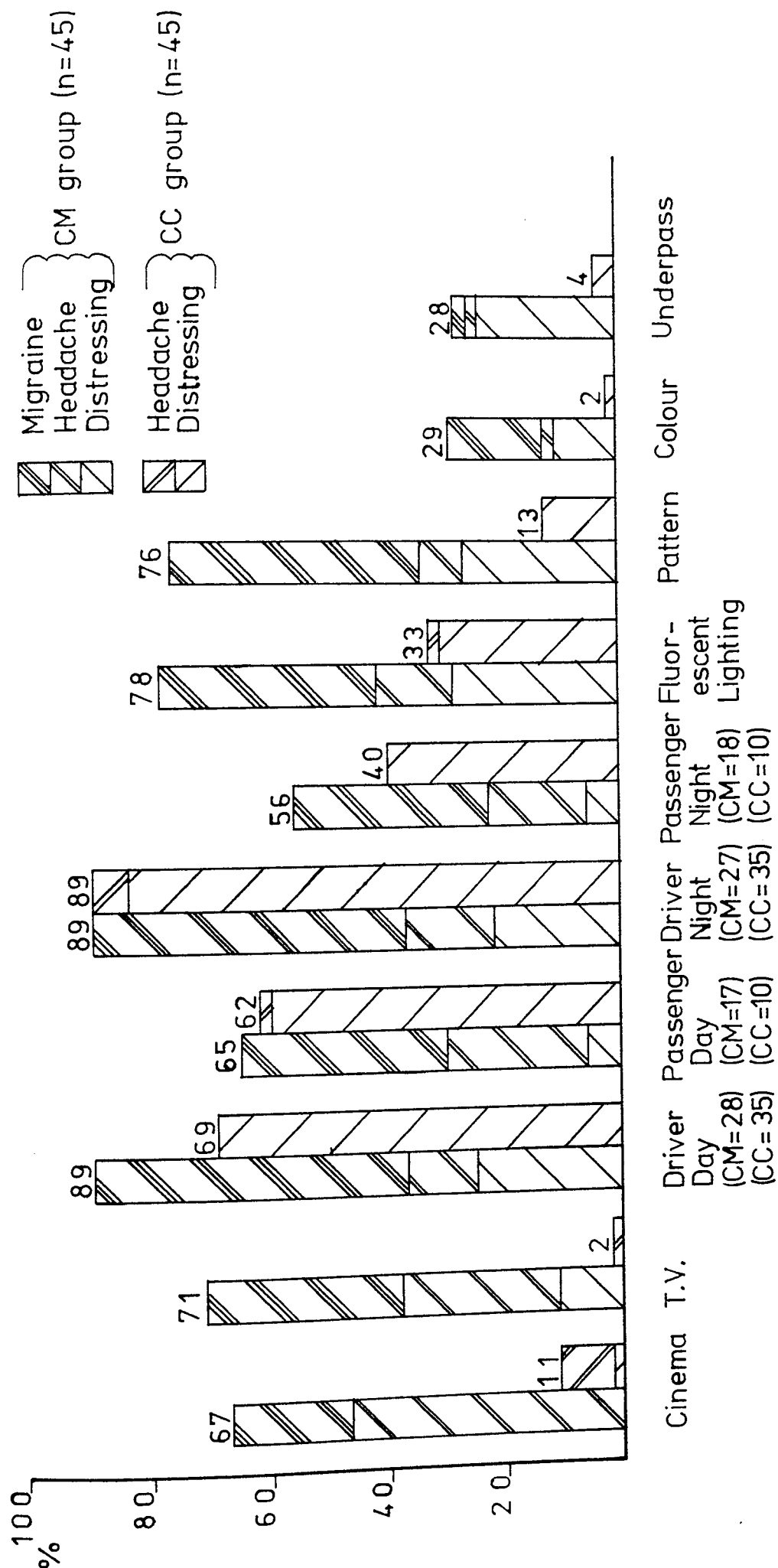


FIG. 2.8 Visual precipitants affecting the migrainous patients (CM) and their age- and sex-matched controls. (See text for details).

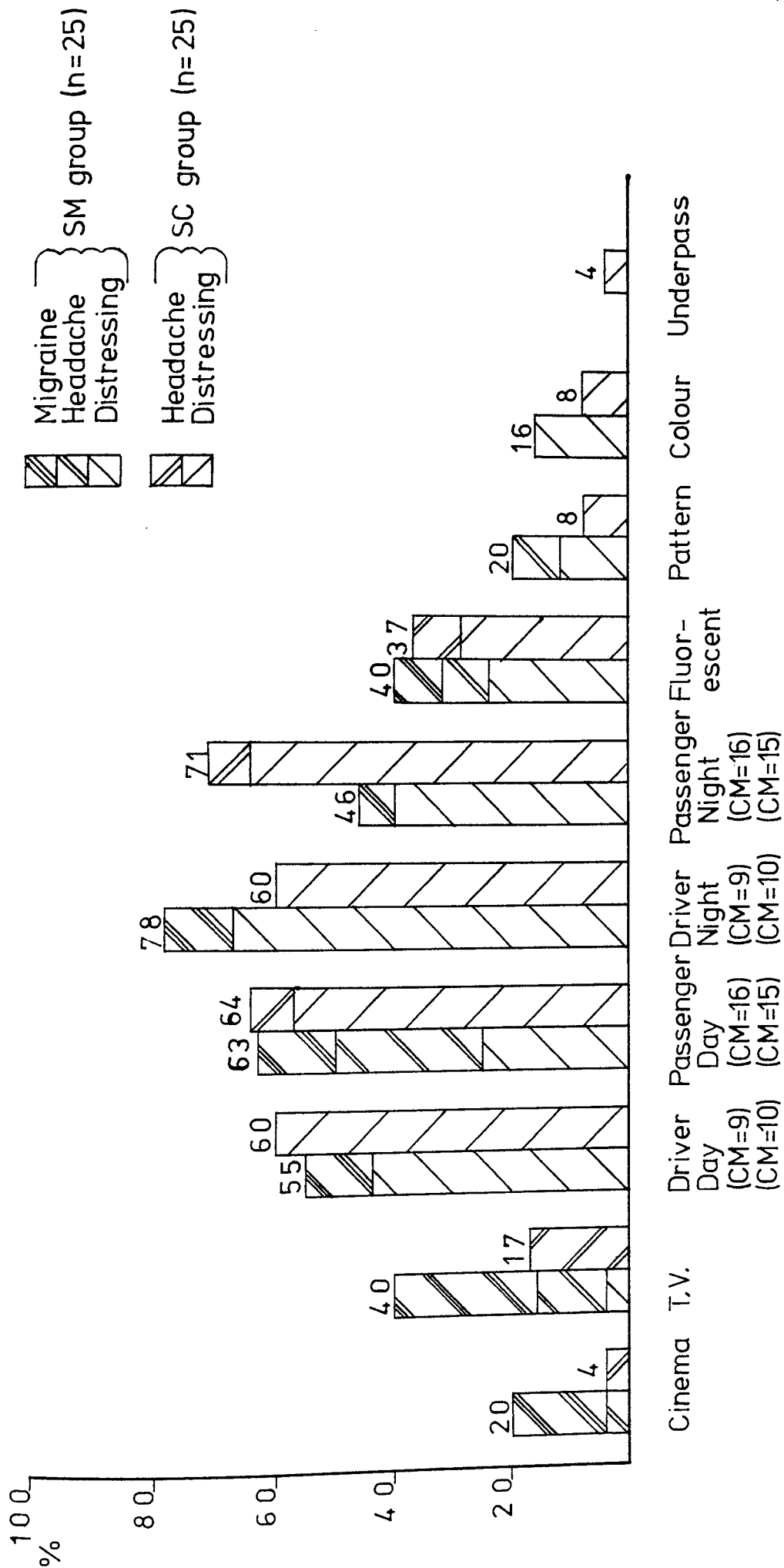


FIG. 2.9 Visual precipitants affecting the migrainous students (SM) and their age- and sex-matched controls (SC).

"uncomfortable" or "like I do at the early part of a migraine". The remainder were asked to make this distinction. It is possible that some of the migrainous do not report as distressing feelings reported as distressing by controls, in that, for example, many of the control subjects reported they disliked oncoming headlights, particularly undipped ones, because they "could not see properly" and they found this "annoying" or "irritating" but apart from the visual stress no other symptoms were experienced. Bearing this in mind the different visual stimuli will now be considered. People co-operating in the study groups (CM, CC, SM, SC, SF) are identified by a code number and additional Clinic patients interviewed are coded alphabetically.

The semi-structured interview was intended to elicit information rather than provide a highly specific checklist, so while some of the information can be presented as affecting a known proportion of the samples (e.g. cinema and television) much of the information was in the form of spontaneous comments (e.g. responses to the questions on day and night travel) and is therefore presented in the text below in the form of examples.

Cinema viewing affected 20% of the CM group and 16% of the SM group to the extent of causing migraine, while 49% of CM and 4% of SM found "ordinary headaches" followed a cinema visit. Two CM (25, 72) and one SM (97) had ceased going to the cinema because of attendant migraine. One SM (100) with cinema triggered migraine and four CM (two with migraine (6, 13) and two with headache (27, 63) from a cinema visit) reported they were less affected if they sat further back in the cinema, these spontaneous comments echoing those reported by Bille (1962). An additional patient (A) commented that his susceptibility increased when screens got "bigger and brighter", which

coupled with the preceding comments would seem to implicate the area of the retina stimulated as being of importance. That this is not the sole factor is indicated by other comments (see Table 2.11). Three clinic patients (J, 8, 63) were especially affected if the camera zoomed in and out or if the subjects or background on the screen moved rapidly (the role of passive motion was considered earlier in section 1.6.9 and 1.6.10) and one of these (CM8) also commented that "the longer the film the more likely the migraine", a comment also made by one of the SM (99).

That visual stimuli are not the only factors operating at the cinema was also made clear. One CM (60) and three CC (33, 75, 79) complained about noisy films, with three of them regarding the noise as the precipitant of migraine (CM60) or headache (CC 33 and 75) and the fourth (CC 79) finding noise distressing, not the visual factors. One further CM woman (59) mentioned that a 'gripping' film, if it caused emotional tension often produced a tension headache but that she also had migraine to films when she was unaffected by an emotional response. Finally, one CM (8) specifically stated that if she "felt fragile" then a visit to the cinema invariably produced migraine. (A number of patients used this phrase to describe how they felt when they were bordering on attack but had not crossed the threshold, and if careful could avert an attack).

Similarly television was specifically mentioned by CM (8) as only affecting her when she 'felt fragile' and CM (20, 62, 64 and 70) and SM (93 and 103) found television turned an ordinary headache into migraine and exacerbated a migraine attack. This and other aspects of television triggering are shown in Table 2.12. As with cinema

TABLE 2.11      Aspects of cinema viewing promoting or precipitating discomfort, headache or migraine, specifically quoted by subjects

(CM - Clinic Migraine; CC - Clinic Controls; SM - Student Migraine; SC - Student Controls; Alphabetical - patients interviewed but not included in the CM group). None of the SF (student headache free) group were affected.

<u>Aspect</u>	<u>Subjects</u>
Too near screen	CM (6, 13, 27, 63) SM (100)
Bigger and brighter screen	Patient (A)
Zooming or rapid movement	Patient (J) CM (8, 63)
Long film	CM (8) SM (99)
Emotion	CM (59)
Sensitized period	CM (8)
Noise	CM (60) CC (33, 75, 79)

TABLE 2.12

Aspects of television viewing promoting or precipitating discomfort, headache or migraine - specifically quoted by subjects

(CM - Clinic Migraine; CC - Clinic Controls; SM - Student Migraine; SC - Student Control) None of the SF group (students free of headache) were affected.

<u>Aspect</u>	<u>Subjects</u>
Extra bright	CM (8, 64)
Zooming or rapid movement	CM (8, 11, 13, 16, 18, 23, 56)
Flickering (special effect)	CM (8, 23, 57, 60) CC (90)
Unlit room	SM (82) SC (121)
Watching "too long"	CM (8, 13, 22, 25, 57, 60, 61, 72) SM (91, 104, 105, 107) CC (166)
If tired	SM (100, 107, 108)
Sensitized period	CM (8, 60)
Exacerbates	CM (8, 20, 62, 64, 70) SM (93, 103)
Noise	CM (3, 13, 15, 67, 72) SM (107) CC (78) SC (176)



both brightness and "zooming" were specified with the addition of flickering when used as special effect, with three CM (8, 13, 18) specifically complaining of the zooming or flickering used in Top of the Pops and three others (8, 16, 58) of the swirling pattern "used in the Ajax advert". Length of watching was an important factor with "too long" varying from "starts to affect me immediately" (CM 8, 22) through one or two hours (CM 72 and 25 respectively) to three or four hours. The state of the individual also affected susceptibility to migraine with tiredness or an already present NMH being two aspects. Under "sensitized period" one CM (8) was affected when "feeling fragile" and the other CM (60) was especially sensitive from pre-menstruation to just post-menstruation, and it was earlier noted in section 1.6.7 that this is the stage of the menstrual cycle when women appear to be most at risk to migraine. Again, noise may play a part, see Table 2.12, with CM (15) and SC (176) complaining of the high pitched background noise which they found distracting but not unduly distressing and all the others being affected by a loud volume of sound. Bille (1962) reported that the children with pronounced migraine that he studied could reduce their attacks precipitated by TV by viewing in a lit rather than an unlit room, a factor mentioned by only two subjects in this study (SM 82 and SC 121) but since subjects were not specifically asked about lighting when viewing, this may under-represent the number so affected.

With both cinema and television viewing the proportions of the CM and SM groups affected to the extent of having migraine are similar, although considerably more of the CM group report headache or discomfort in both conditions. This pattern does not reoccur in other conditons, however, where the CM group consistently report a considerably greater

incidence of migraine. One might assume an equivalent exposure in all groups, including the controls, to fluorescent lighting, pattern and colour. However, this is by no means the case with car travel for a smaller proportion of students could drive and many did not have access to car travel during term-time, which reduces both their exposure to car travel and the chance of recall of events, since the time lapses would be greater. However, since the overall picture, comparing Fig. 2.8 and 2.9 is one of increased susceptibility to all factors we could assume this susceptibility plays the major role in car travel.

As motion sickness has been suggested as a possible precipitant (see section 1.6.9) a note was made of comments relevant to this, see Table 2.13, and there was no significant difference in malaise between the migrainous and their matched controls. Four subjects could travel happily in a well-ventilated vehicle but not in one with a stuffy atmosphere, a reaction compatible with findings on stuffy atmospheres noted in section 1.6.8. Four migrainous and three controls preferred coach travel to car travel and although the students simply said they were less travel-sick, the two in the CM group gave an alternative explanation. This explanation was that when travelling by car they became very tense and anxious, partly due to fear of accidents, which caused their reactions, with CM 60 experiencing migraine. A considerably greater number were affected only by coach travel, which might suggest that differences in vehicle motion or a stuffy atmosphere were at fault. However, an alternative explanation is consistent both with findings on passive motion, mentioned earlier, and with effects of zooming on cinema or television screens. This explanation is that in coaches most passengers are forced to look sideways where they will

TABLE 2.13      Aspects of travel sickness quoted by subjects

(CM - Clinic Migraine; CC - Clinic Controls; SM - Student Migraine; SC - Student Control). None of the SF (student headache free) group were affected.

<u>Aspect</u>	<u>Subjects</u>
Feel unwell, can produce nausea and vomiting	CM (3, 9, 13, 14, 17, 19, 20, 22, 60, 61, 68, 72) SM (92, 93, 95, 96, 98, 99, 100, 101, 103, 104, 105, 107, 109, 149, 152, 153) CC (31, 34, 37, 40, 43, 46, 48, 50, 51, 79, 80, 84, 85, 86) SC (114, 120, 121, 123, 124, 126, 131, 132, 166, 167, 168, 169, 170)
Stuffy atmosphere	CM (9) SM (101, 107, 150)
Prefer coach to car	CM (17, 60) SM (93, 107) SC (166, 167, 169)
Affected only by coach	CM (13, 14, 19, 22, 61) SM (96, 98, 100, 103, 104, 149) CC (34, 40, 48, 84, 85, 86) SC (120, 121, 124, 131, 132)
Car: sick as passenger, fine as driver	CM (9, 13, 20, 68) SM (92, 95, 105, 154) CC (37, 43, 46) SC (126, 168)

see the landscape zooming past. Such an explanation is supported by the following comments from various subjects. SM 105 specifically said that if he can look ahead in coaches or cars he is not travel sick but looking sideways out of cars, coaches and trains results in sickness, sometimes accompanied by headache. Similarly CM 70 and SC 168 were happy driving but found it distressing when travelling by coach or train and forced to look sideways, with SC 168 also affected as a back seat car passenger. SM 154 ceased to be troubled by migraine or travel sickness on journeys once she learnt to drive, if she "back-seat drives and watches the road". Two passengers, CM 16 and CC 34 were distressed by looking sideways, with CM 16 experiencing migraine if she looked sideways for long.

Examining the visual factors the data in Fig. 2.8 and 2.9 was presented separately for drivers and passengers since many passengers said they shut their eyes, looked away or took other preventative measures. For example, CM 8 when a passenger at night, ties a thick scarf over her eyes if there are many oncoming headlights and if driving she, like CM 24, takes preventative medication before lengthy journeys.

The situations mentioned as causing migraine, NMH or discomfort during day travel included, as expected, bright sunny days with their associated reflected glare, sunlight shining through an avenue of trees or railings and travelling towards a low sun. What was not expected were the comments, which were reported mainly by the CM group, on four other aspects.

- (a) Seven of the CM group were affected by the flashing of brake-lights or indicators of the car in front, especially in queues of traffic such as at traffic lights, or at junctions, with this effect being more marked at night. Flashing indicators could produce migraine in CM 9, NMH in CM 18 and were distressing to CM 58. Brake-lights could precipitate migraine in CM 24, headache in CM 57 and were distressing to CM 8 and 72. CM 72 finds the extra bright additional brake-lights fitted on some cars especially distressing and CM8 feels impulsively attracted to brake-lights reporting that they 'draw' her.
- (b) Impulsive attraction was noted not only by CM 8 (see above) but also by CM 58, "I want to drive into oncoming headlights" and by CM 13 "I want to drive towards bright streetlights".
- (c) Flashing neon advertisement signs distressed CM 3 and CM 58 at all times and SM 46 at night.
- (d) Road and lane markings were reported as factors only by drivers with Patient N and CM 6, 13 and 14 having had migraine triggered by the yellow stripes painted across some dual carriageways on roundabout approaches; these distressed Patient L and CM 24. CM 72 was troubled by the white stripes painted across part of the centre of the road to protect traffic turning right at T-junctions, and had had migraine triggered when driving past these. Two of the CC group and one of the SC group were irritated by the white lane markings and CM 27 also found them distressing, especially when reflected in the car windows.

The data for night travel, in Fig. 2.8 and 2.9, represents with one exception the reactions of people to oncoming headlights. About one-third of the migrainous and one-third of the control subjects commented that undipped or badly adjusted dipped headlights had more of an adverse affect, and three of the eight in the SF group commenting they disliked undipped headlights. Such comments could be expected, as could the one that wet roads increased the dazzle effect of oncoming headlights, indeed such conditions made the reflections of their own headlights unpleasant for CC 28 and 43 and could precipitate migraine in CM 13. SM 98 was not affected by oncoming headlights (he is the exception mentioned above) but he, like some others, employed the strategm of watching the gutter to avoid looking at undipped or badly adjusted headlights. SM 98 was, however, affected by headlights, especially undipped ones, reflected in the driver's mirror, this situation produced migraine in CM 27, NMH in CM 1 and was distressing to SM 98 and SC 124, 172 and 176. Some drivers had fitted adjusting or 'dipping' mirrors to remove this problem.

In the case of vehicular tunnels not everyone had used these, but in those who had and who were adversely affected, the majority complained about the lighting at the kerb as one enters and leaves which produces a flicker effect on driving past. A few were also concerned about the spaced overhead lighting in long tunnels which produced alternating patches of light and shade, thus producing a flicker effect when driving through. This provoked headache in one of the CM groups (CM 6), and migraine in another (CM 10). The effect of both types of lighting was heightened at night.

Fluorescent lighting affected 78% of the CM group which was almost twice the percentage of the SM group so affected (40%). The control groups were less affected with 33% of the CC group being affected and 37% for the SC group. Those disliking fluorescent lighting found it "too harsh", "too glaring" or were aware of the flicker in unshielded tubes even when "working properly". In the CM group who reported migraine to fluorescent lighting eight were triggered when the lights were working adequately with a further eight affected if the tube is not working properly and is 'flashing'. Three of this latter group can have migraine triggered if they are in a room when a fluorescent lamp is switched on, if it flashes several times. While the two from the SM group both reported migraine was induced only by the flashing of faulty tubes. On the other hand five of the SM group preferred fluorescent lighting to central bulbs because the tubes give "a good light and get rid of shadows". Perhaps this preference for the removal of strong contrast reflects a phenomenon more clearly seen in the response to patterns, especially strongly contrasting ones.

Following from the comments on road markings and the reports of Williams (1972), Grist (1972) and Speer (1975) discussed in section 1.6.10 one might expect striped patterns to be most often reported as a problem and this is the case, as illustrated in Table 2.14. Vertical stripes were more often a problem than horizontal stripes and three people affected by both types specifically declared that vertical stripes affected them more than horizontal stripes. It is suggested this is consistent with the point made by Lyle (1969) "that vertical ocular movements are much less commonly employed than lateral movements" and the findings of various workers, notably Hubel and Wiesel, on pattern recognition cells in the visual system (see Lindsay and Norman, 1972). A horizontal eye movement across vertical stripes would

TABLE 2.14

Number of migrainous people in various groups finding particular patterns distressing to look at (D), could produce a headache (H) or could precipitate a migraine (M).

The groups being clinic patients interviewed but not included in the CM group; patients from the Migraine Clinic in the study group (CM); and the group of students with migraine (SM).

Pattern	Patients not CM n = 14			CM n = 45			SM n = 25		
	D	H	M	D	H	M	D	H	M
Vertical stripes	5		5	9	1	7	2		
Horizontal stripes	1		1	3		5	2		
Checkered	4		1	5		5		1	
Grid	2			1	1	2		1	
Diamonds				3	1	1		1	
Diagonals				1					
Zig-zag			2	7		5	1	1	
Concentric Star				1			1		
Spiral	1			7	2	4	2		
Spots	3		1	5		6		2	
Linked, looped				2					
"Busy"						1			
Total no. affected by any of the patterns and percentage of group	10 (71%)			34 (75%)			5 (20%)		



activate more of these pattern cells than a movement along a horizontal stripe. The activity of such cells would also be consistent with the finding that other patterns complained of (see Table 2.15) almost all consisted of patterns with clearly defined corners such as the grids and checks. Judging from the description the two people complaining of "busy" patterns were describing "op art" patterns which tend to be visually stimulating in the pattern sense. The exceptions to patterns involving lines and corners were spots and spirals.

With spots SM 107 commented that spots in an irregular pattern did not trouble him, but if arranged in a regular (grid) formation he perceived them as rows or columns of spots which then had the same effect as horizontal or vertical stripes, that is making him queasy, and could provoke a headache. Whether this effect occurs in the others finding difficulty with spots is unknown.

When examining references to situations where the patterns were found to be distressing or a migraine precipitant they were principally clothing (especially when ironing or sewing) and wall paper; but people were also affected by curtains; flooring; zigzag aerial on windscreen (CM 10) and going through a car wash with the brushes banded in black and white (CM 63). In the latter two cases the associated movements of the environment could contribute to discomfort, as previously discussed. Movement was also a factor in sensitivity to spirals with CM 8, 16, 56 and 61 and SM 100 being more affected if these moved and all quoted the "Ajaz" advert with the rotating white 'Tornado' filling the screen as an example of this, with CM 8, 16 and 56 being affected by a non-moving spiral. The other subjects giving a spiral as an example did not mention movement.

TABLE 2.15

Number of non-migrainous subjects in various groups finding particular patterns distressing to look at (D), could produce a headache (H).

The groups being controls for the migraine clinic group (CC); non-migrainous students (SC) and headache-free students (SF).

Pattern	CC n = 45		SC n = 24		SF n = 8	
	D	H	D	H	D	H
Vertical stripes	2		1			
Horizontal stripes	2		1			
Checkered	1		1			
Grid						
Diamonds						
Diagonals						
Zig-zag	1					
Concentric star						
Spiral						
Spots	1		1		1	
Linked, looped						
"Busy"	1					
Total no. affected by any of the patterns and percentage of group	6 (13%)		3 (13%)		1 (13%)	

In the previous literature Grist (1972) referred to the effects of "dazzle patterns" and all the controls complaining about patterns (Table 2.15) described them either as dazzling (particularly stripes), or irritating. Some of the migrainous also described stripes as 'dazzling' but only one specifically mentioned the high contrast road signs mentioned by Grist (1972), CM (6) found that a high contrast "black and white arrows" road sign, if close to the road, always made her feel queasy when being driven past, and if she was "feeling delicate", i.e. bordering on an attack, this would immediately precipitate it.

So far a number of patterns have been described, and the pattern perception processes referred to, two other factors, also consistent with the functioning of these cells, were volunteered. These are that the stronger the contrast the worse the effect, with black and white patterns found especially provoking or distressful (Patient A, CM 12, 61, 63, 64, 68, 70, CC 31, SM 93, SC 169, 176); and that finer patterns of stripes and checks were more troublesome than coarser ones (CM 55, 62, 69). Some of the control subjects found certain patterns distasteful or distressing but were not any further affected (see Table 2.15). Previously the possibility of a graded response was suggested and the data on patterns shows this trend with all control groups having 13% distressed by patterns, the migrainous students having 20% affected with either distress or headache, and the two groups of patients both having just over 70% affected (some of whom had migraine precipitated and others headache or distress provoked). Whether this trend in numbers of individuals affected and the severity of effect would hold true if both the samples of students had been larger and a more detailed structured interview or question-

naire on patterns and their effect used, is a matter for speculation.

Finally, colour was reported as having an effect by 29% of the CM group, 20% of the SM group, 2% of the CC group and 8% of the SC group with none of the SF group adversely affected by colour.

Referring to Table 2.16 the second largest group recorded is "fluorescent or extra bright colours", CM 13 describing these as "extra bright yellow, green, purple and especially the fluorescent range of workmen's jackets." Moreover both SM 152 and 154 stated that the colour yellow had to be a bright yellow to become "painful to look at", a comment also made by SM 99 about orange, SM 103 on the other hand complained about deep purple being distressing. The main colours complained of were red or pink; CM 7 having a migraine each time she tried sewing some salmon pink dress material, with shocking pink similarly affecting CM 61 and 66; the remainder were affected by red, with CM 26 and 65 being made migrainous by "bright red". Of the fourteen patients interviewed but not included in the CM group, four complained of colour, two spontaneously, and for all four the trouble was caused by red. Patient D discovered her sensitivity after she and her husband had "a lovely red carpet" laid in the one room, because afterwards she could not sit in the room without being ill. Being uncertain whether the reaction was to the colour or an allergy to carpet fibres they turned the carpet back and Patient D was then symptom free. Reluctantly Patient D had to get rid of her carpet.

In conclusion, the data on visual stimuli indicate that it is not solely bright light, glare and flicker that cause difficulty but also certain patterns and bright colours (principally red), although these tend to cause discomfort and nothing more serious. The data on patterns is firstly, consistent with activation of the pattern

TABLE 2.16      Colours and the subjects they affected.

None of the SF (student headache free) group were affected.

(CM - Clinic Migraine; CC - Clinic Controls;  
SM - Student Migraine; SC - Student Controls)

<u>Colour</u>	<u>Subjects</u>
Red (or pink)	CM (7, 26, 56, 60, 61, 65, 66, 69, 71) CC (75) SC (172, 177)
Bright Orange	CM (13, 69) SM (99)
Bright Yellow	CM (13) SM (152, 154)
Purple	CM (13) SM (103)
"Fluorescent" or extra bright colours generally	CM (2, 12, 13, 19, 61) SM (95, 154)

perception mechanisms and secondly, shows a gradation of response from the Migraine Clinic patients, through the migrainous students, to the control subjects both in terms of the percentage of people affected and in the severity of the reaction. On all the other aspects examined some of the control subjects were caused discomfort or headaches by them, which again might indicate a gradation of response rather than a clear dichotomy, particularly as the data for the SM group, who could be expected to suffer less severe migraine showed a smaller proportion to be susceptible than the CM group to migraine from these factors, and more closely resembled their age- and sex-matched controls. This suggests the susceptibility to be altered rather than an age factor to be at work. Additional support comes from the statements made by a number of the CM group that certain factors only affect them when they are feeling 'fragile' or 'delicate' and yet can be blissfully unaffected at other times, so they themselves show a graded response, which presumably depends on their internal environment and its metabolic state.

### 2.5.3 Visual precipitants in migraine compared with those of PSE

From the preceeding examples given above and the details for visual stimuli for PSE given in section 1.9.9 it is apparent that there is considerable overlap between PSE and visually precipitated migraine as regards the types of visual stimuli, which can affect the two groups. There are, however, some exceptions as can be seen in Table 2.17 which is an amendment and enlargement of Table 1.8 in the light of the findings of this study. Of the items that appeared in Table 1.8 as inducing migraine each one was mentioned as a precipitant by at least one of the CM or SM groups. Some of the items included in Table 2.17 were not discussed in section 2.5.2 but were mentioned

**TABLE 2.17** A comparison of the types of visual stimuli reported to affect photosensitive epileptics with those reported in the literature and found in this study to induce migraine (see text, section 1.9.9 and sections 1.6.10 and 2.5.2 respectively)

Visual Stimuli	PSE	Migraine
<b>1. <u>Sunlight</u></b>		
bright sunlight itself		x
low direct sun		x
through leaves of trees	x	
through helicopter blades	x	
reflected off snow	x	x
reflected off sea or water	x	x
reflected off metal	x	x
reflected off white walls		x
reflected off paper		x
through white clouds		x
travelling down avenues of trees	x	x
travelling past railings	x	x
travelling past bridge or tunnel columns		x
<b>2. <u>Artificial light</u></b>		
oscilloscopes	x	
stroboscopes	x	x
blades of mechanical saw	x	
fluorescent lighting	x	x
fairground lighting	x	x
amusement arcade lighting	x	
flashing neon signs		x
cinema screen	x	x
TV screen	x	x
microscopy		x
vehicular tunnels - side lighting	x	x
vehicular tunnels - overhead lighting		x
Headlights - oncoming		x
- reflected in driver's mirror		x
Brake lights		x
Car indicators		x

TABLE 2.17 CONT'D.

Visual Stimuli	PSE	Migraine
3. <u>Pattern</u>		
Vertical Stripes	x	x
Horizontal Stripes	x	x
Checkered	x	x
Grid	x	x
Diamonds		x
Diagonals	x	
Zig-Zag		x
Spiral	x	x
Spots		x
4. <u>Colour</u>		
Red	x	x
Orange		x
Yellow		x
Purple		x
"Fluorescent" or very bright colours		x



as other visual stimuli inducing migraine either spontaneously or in response to the final general question in FQ.

Such a comparison between lists of possible trigger factors gives the superficial impression of close similarity, an impression belied if one examines the proportions of the two types of patients affected by different groups of factors as shown in Fig. 2.10. It should be noted that the size of the sample of photo-sensitive epileptics is ten times the size of the Migraine Clinic sample but it is unlikely that such enormous differences as those displayed in Fig. 2.10 would become non-significant with an increase in the size of the migraine sample.

The most provocative stimuli for migraine attacks are clearly artificial light (both indoors and outdoors), sunlight (direct or interrupted) and patterns, yet less than 10% of photo-sensitive patients have fits from these causes. For PSE the most common precipitant is television (66% affected) yet only 33% of migraine patients regard this as a precipitant.

Colour does not appear in Fig. 2.10 as Jeavons and Harding (1975) did not report any of their PSE patients as being unduly affected by colour. In contrast 16% of the migraine patients considered colour to be a provoking factor of attacks.

A further difference between PSE and visually induced migraine becomes apparent when a close examination is made of the responses of drivers and passengers going down an avenue of trees or past railings on a sunny day. In section 1.9.9 it was noted that no drivers have been

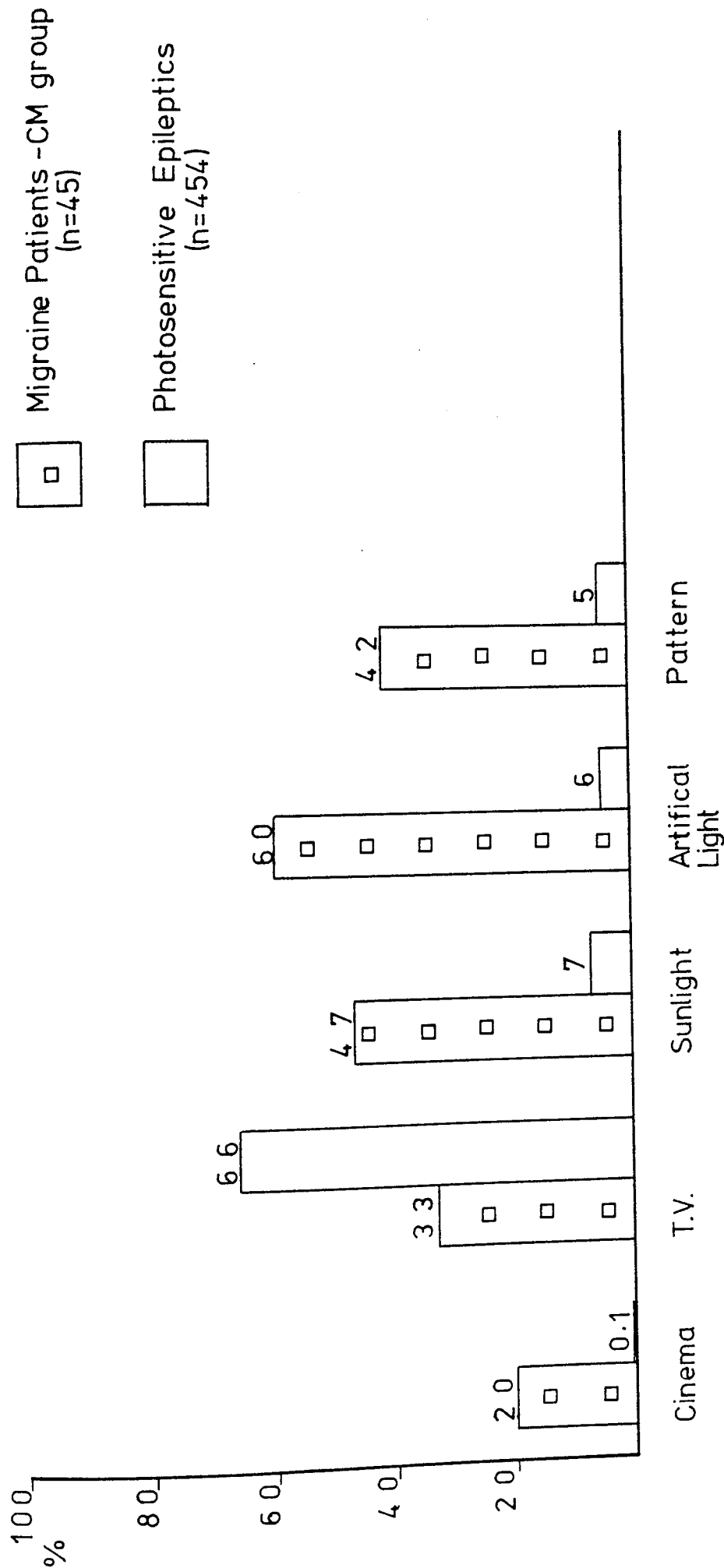


FIG. 2.10 Visual stimuli precipitating migraine in 45 patients with visually induced migraine with figures for visual stimuli precipitating photo-sensitive epilepsy reported by Jeavons & Harding (1975).

reported as having fits induced in this situation, although passengers have had fits. It has been suggested (Jeavons, Harding and Panayiotopoulos, 1971; Jeavons and Harding, 1975) that drivers of cars would not get fits in such a situation as lateral illumination does not evoke abnormal discharges in the EEG during IPS. However, as can be seen in Table 2.18, both drivers and passengers can have migraine induced in this situation and a greater percentage of the drivers, rather than passengers, are so affected. If one includes those who are distressed or are having an ordinary headach induced, then in both the CM and the SM group a greater percentage of drivers are affected. If these two groups are combined the differences in percentage of drivers, as compared to passengers, affected is not significant ( $p < 0.25$ ). The figures for the control groups are included as they show that some of these people are affected by the situation under consideration. The control subjects affected found the situation distressing, but no worse, and again there is an overall trend for drivers to be more affected although the difference is not significant. Thus in this particular situation the migraine group are unlike the PSE group and show a similar trend to the control group in that it is drivers rather than passengers who are affected.

In conclusion, it once again appears that an apparent similarity between PSE and visually induced migraine is only superficial. On closer investigation the apparent overlap between the types of situations precipitating PSE or inducing migraine yields two major differences:

- (a) the proportion of patients affected by any of the groups of precipitant factors is very different in the two conditions (i.e. PSE or visually induced migraine).

**TABLE 2.18** The effect of sunlight shining through an avenue of trees, railings or the columns of bridges or tunnels, on the migrainous patients and students, and their controls.

Reaction	CM group				SM group			
	Passenger		Driver		Passenger		Driver	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No effect	15	(79)	17	(66)	12	(75)	5	(56)
Distressing	1	( 5)	4	(15)	1	( 6)	3	(33)
Headache	1	( 5)	1	( 4)	2	(13)	0	( 0)
Migraine	2	(11)	4	(15)	1	( 6)	1	(11)
Total	19	(100)	26	(100)	16	(100)	9	(100)
Total affected	4	(21)	9	(34)	4	(25)	4	(44)

Reaction	CC group				SC group			
	Passenger		Driver		Passenger		Driver	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
No effect	9	(90)	26	(74)	12	(86)	9	(90)
Distressing	1	(10)	9	(26)	2	(14)	1	(10)
Headache	0		0		0		0	
Total	10	(100)	35	(100)	14	(100)	10	(100)
Total affected	1	(10)	9	(26)	2	(14)	1	(10)

- (b) macular illumination appears essential to precipitate PSE, but lateral illumination from a flickering source can induce VIM, which implies involvement of the peripheral part of the retina.

## 2.6 Electrophysiological recordings - equipment and method

For convenience the information below is written to follow the course of the procedure, with details of the equipment used, factors controlled and the development of the method being given at the appropriate points.

### 2.6.1 Selection of subjects

This has already been described in section 2.2 but additional checks were made at the time of recording on whether the subject was affected by any factors that would merit the exclusion of that subject (see below).

### 2.6.2 Experimental preliminaries

Prior to the subject's arrival the equipment was set up and initial calibrations carried out (see below for details). When the subject arrived he/she was taken into the subject room and seated on a low chair (for convenient application of electrodes). The experimental procedure was briefly outlined and any queries answered. As the experimental procedure progressed at each stage instructions were given and any necessary explanations made.

Each subject was asked for certain items of information as follows:

- (a) As it is thought transient EEG changes may follow migraine in some cases (see section 1.10), all subjects were asked if they had had a headache in the previous fortnight. If so, they were asked firstly for the date of their last headache and, secondly, about the symptoms of that headache.

- (b) The clinical history was checked regarding a history of epilepsy and head injury. This was considered necessary as in one of the pilot runs a young man was found to have fractured his skull in the right occipital region two years earlier, but he had not marked this as a severe head injury on the questionnaires. In his case no abnormalities were found in the recordings.
- (c) Subjects were asked what medication they had taken in the previous ten days as medication can affect the EEG (see section 1.8).
- (d) Women were asked for the date on which their last menstrual period had started. Ideally the experiment would have been designed to control for stage of the menstrual cycle (see section 1.8), especially as the menstrual cycle is thought to affect susceptibility to migraine in women (sections 1.6 and 1.7). However, owing to limitations in time available the availability of the facilities, and the availability of subjects, it was not possible to control this factor. It was therefore assumed the women in the groups compared would show random variation with regard to the dates of their last monthly periods and so the groups would be balanced for this effect. The date of their last menstrual period was obtained so that an appropriate assessment of their basic EEG could be made, see section 1.8.

- (e) Subjects were asked when they had last eaten. Any subject who had gone more than three hours without food was given sweetened tea or coffee or a glucose drink. This excluded the possibility of hypoglycaemia influencing the recordings (see sections 1.8 and 1.10) or of precipitating a migraine (see section 1.6) when it was VM that was the object of study.

Subjects who brought a completed HQ2 (see section 2.1) with them were asked for this and HQ2 was checked. Subjects who had not fully completed HQ2 were asked to do so while the electrodes were applied. Migraine patients had completed the semi-structured interview using FQ at the Clinic (see section 2.1), all other subjects were given the same semi-structured interview while the electrodes were applied, and if necessary it was completed at the end of the session while the electrodes were being removed.

Silver/silver chloride disc electrodes (Cooper, Osselton and Shaw, 1974; Scott, 1976) were attached to the scalp with collodion glue and filled with a conducting jelly. They were placed according to the International 10-20 system (see section 1.8 and Fig. 1.3). A full head of electrodes was not applied for the following reasons. In the preliminary study (Debney, 1973) a number of the patients (an exact figure was not recorded) had particularly tender spots on the scalp at the site for electrodes  $F_7$  and  $F_8$  and to a lesser extent at  $T_5$  and  $T_6$ . Selby and Lance (1960) noted tenderness of the scalp during or after the headache in two-thirds of their patients and Hay (1976) reported pain trigger areas in migraine, one of which corresponds well with the site of  $F_7$  and  $F_8$ . The necessary skin drilling to reduce



the resistance of these electrodes below 5 kohms produced marked discomfort or pain in such patients, who became visibly tense and their elevated scalp muscle tension created problems with muscle artefact in the EEG. Therefore the use of these sites was abandoned. Without these electrodes a transverse montage was much reduced in usefulness, therefore electrodes  $F_z$  and  $P_z$  were also not used, with  $C_z$  retained for use as an earth electrode.

After the electrodes had been applied and their resistances adjusted to below 5 kohms the subject was transferred to a bed, which had pillows to support the subject's head. The electrodes were plugged into a headbox which was connected to the recording equipment outside the subject room. The subject room was lit only by artificial lighting which was adjusted to an intensity of 2 candelas/m<sup>2</sup> just before the start of the recording of the basic EEG, and kept at that level throughout the experimental procedure so the eyes remained light adapted (for reasons see section 1.8). Throughout the experiment the subject was monitored from the recording room by means of a closed circuit television (CCTV). Subjects were told they were being monitored by CCTV because it was hoped this would both reassure subjects that care was being taken of them, and discourage any straying of attention or non-compliance with instructions by the subjects. The subject room was sound-damped, however the door to the recording room was left slightly ajar so that the subject could hear specific commands from the experimenter.

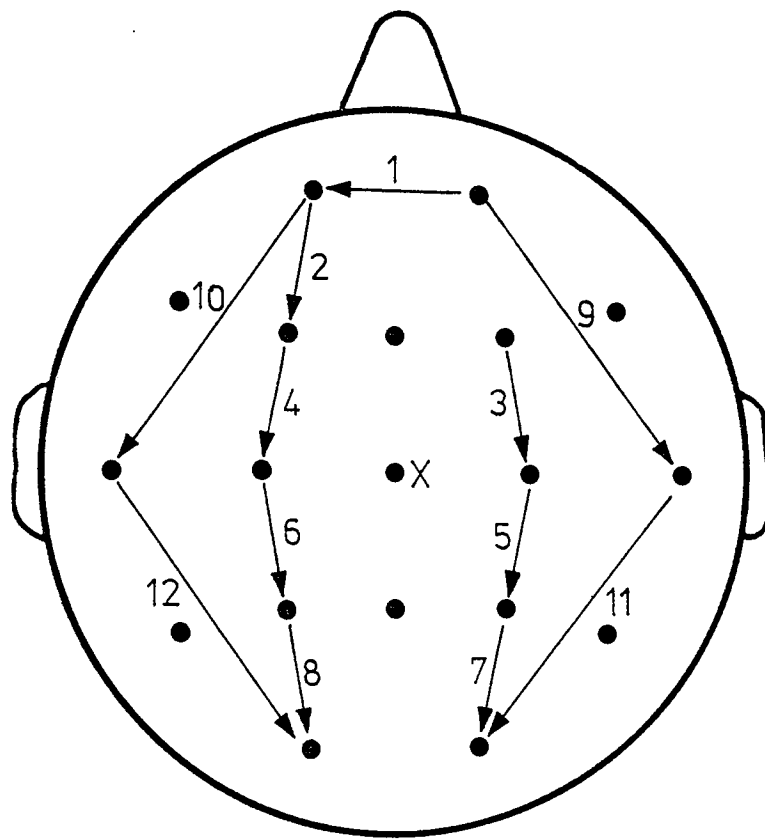
### 2.6.3 Recording the basic EEG

The EEG was recorded on a 12-channel S.L.E. electroencephalograph. A pen write out was obtained at a paper speed of 30 cm/sec., with the machine set to record at a time constant of 0.3 and gains of 3 and 4. Before recording the basic EEG the following steps were taken:

- (a) the experimenter went into the subject room and briefly outlined the procedure to be followed and instructed the subjects to follow each direction as it was given. They were reminded they would be monitored by the CCTV.
- (b) the machine calibration was checked to ensure it was at 100 microvolts/cm.
- (c) a biological calibration (all channels recording between two standard electrodes,  $O_2$  and  $F_4$  in this case) ensured all channels were equally responsive.
- (d) the montage was checked. The montage used is shown in Fig. 2.11. Originally channel 1 had been set to record between  $Fp_2$  and  $F_4$  but was changed to the setting shown in Fig. 2.11 with the aim of monitoring tension in the frontalis muscle (see below).

The basic EEG was recorded using the following sequence of events:-

- |                                     |          |
|-------------------------------------|----------|
| (a) Begin with eyes open (EO)       | 10 secs. |
| (b) Eyes closed (EC)                | 30 secs. |
| (c) EO                              | 10 secs. |
| (d) EC                              | 20 secs. |
| (e) Keep EC, start hyperventilation | 90 secs. |
| (f) EO continue hyperventilation    | 30 secs. |
| (g) EC continue hyperventilation    | 60 secs. |



X - earth electrodes

FIG. 2.11 Electrode montage (bipolar derivations) used to record the basic EEG on a 12-channel electroencephalograph. (see text.)

- |   |   |
|---|---|
| (h) keep EC, return to normal breathing | 60 secs. or<br>until record<br>returns to<br>previous level |
| (i) EO, normal breathing                | 10 secs.  |
| (j) EC, normal breathing                | 10 secs.  |

#### 2.6.4 Muscle artefact

When recording the EEG difficulties with gross muscle artefact occurred in some subjects, such that the introduction of high frequency filters set at 50 Hz was not sufficient to remove the artefact. In such cases the recording was stopped and a check on the comfort of the subject was carried out. In some a full bladder or slipped contact lens was the cause, in others an adjustment to pillow height or rearrangement of electrode leads under the head was sufficient to remove the muscle artefact. In others a clenched jaw (as evidenced by artefact predominantly in channels 9 to 12) was the cause. In one subject removal of dentures removed this problem. In the others, and in those generally tense as evidenced by tension of the frontalis muscle, some isometric exercises were necessary to achieve adequate voluntary muscle relaxation. Once recording was restarted subjects were monitored for this tension and instructed to relax or 'let their jaw go limp' as necessary.

#### 2.6.5 Recording of EEG response to IPS

A Grass Photo-Stimulator Model PS22 was used to provide the IPS. This stroboscope gives a blue-white flash, lasting 10 microseconds, of instantaneous peak intensity, the flash frequency being continuously variable. Throughout the experiment it was set at Grass intensity 2 which, according to the manufacturers is approximately 187,000 horizontal candle power measured on the axis of the parabola at a distance

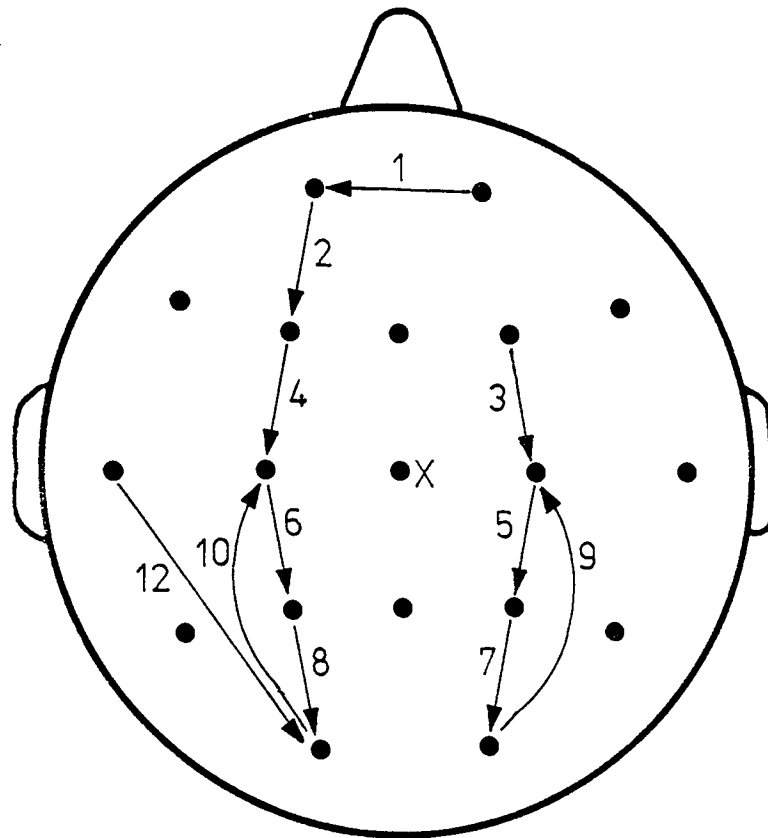
of 2 feet. The lamp was fitted with a diffuser glass (radius 70 mm) and patterns mounted on 3.0 mm thick perspex could be slotted in front of this. The fine grid pattern used to test for PSE was the Normatone fine grid (No. HN 559) pattern (squares approx. 1 mm x 1 mm). The noise of the stroboscope was partially masked by the ventilating fan in the room.

The procedures recommended by Jeavons (1969) were adopted (see section 1.8) and the stroboscope screen was placed 30 cm. away from the subject's eyes in the direct line of gaze. The centre of the screen marked with a small circle to act as a target. The light flashes were monitored on channel 11 of the EEG.

The montage used for recording responses to IPS is shown in Fig. 2.12. This montage is essentially that used by Jeavons and Harding (1975) in their work on PSE and was used in this study as it was wished to investigate whether patients with VIM showed responses to IPS that were similar to those found in PSE. Two modifications of the montage used by Jeavons and Harding were made. Firstly, channel I originally  $Fp_2$  to  $F_4$  was altered to  $Fp_2$  to  $Fp_1$  to again monitor the activity of the frontalis muscle and so excessive tension. The second modification was to retain channel 12 from the basic EEG montage to continue monitoring of excessive jaw clenching.

Originally it had been hoped to incorporate two investigations within the experimental design.

- (a) to monitor the EEG responses to IPS, over a range of flash rates between 30 f/sec. to 1 f/sec., for any responses reported as characteristic of PSE



X - earth electrode  
Channel 11 - strobe monitored

FIG. 2.12

Electrode montage (bipolar derivations) used to record the responses to IPS on a 12-channel electroencephalograph. Channels 9 and 10 were processed through a computer of average transients to produce VEP recordings. Channel 11 was used to monitor the stroboscope flashes. This montage is modified from that routinely used at the Neuropsychology Unit when investigating PSE (see text).

and to inspect VEPs at low rates of flash for occipital spikes (see section 1.9.9).

- (b) to carry out automated frequency analysis (see section 1.8), of the resting EEG and of the photic driving responses to IPS at various flash rates between 5 f/sec. and 30 f/sec. so that a comparison could be made between responsiveness to IPS and the predominance of various frequencies (c/sec.) of the activity in the resting record.

Regretably computer facilities to provide such automated frequency analysis did not become available in time to be used for this study. The Neuropsychology Unit possesses a BNI or Walter type wave-analyzer which uses band pass filters and integrators. Despite the comment of Fukushima (1975) that such analyzers are not reliable enough to analyze photic driving because of artifacts contamination, the use of this analyzer was contemplated. In the event a series of trial runs, intended to test the reliability of the analyzer when processing small time samples (in the range of 5 to 20 seconds), proved the equipment to be faulty with both the tape-recorder and the analyzer prone to frequent breakdown. Thus the use of this equipment was considered a liability rather than an advantage and had to be abandoned for more lengthy methods (see section 2.7).

Thus the final experimental design to obtain the EEG response to IPS was as follows:

- (a) enter subject room and position lamp 30 cm. from subject's eyes,
- (b) check subject's visual acuity, when focusing at the 30 cm. distance (for method see 2.6.6) and ensure subjects having glasses for refractive errors

wear them (a precaution also taken by Lehtonen, 1974)  
so that the fine grid pattern is seen in focus,

- (c) insert fine grid pattern in front of stroboscope,
- (d) inform the subject of the procedure to be followed  
(see e and f) and tell them they will be asked to  
report what effect, if any, the IPS has on them.

This last instruction aimed on the one hand to keep  
the subject's attention high, and so prevent habituation,  
and on the other hand, to extract information on whether  
the IPS produced reports of 'feeling peculiar' (as  
from some PSE patients, see section 1.9.9) or of  
feelings of nausea or other migraine symptoms.

- (e) leave subject room,
- (f) remind the subject to keep their eyes open and to  
look at the centre of the screen,
- (g) present the following flash rates in this order:  
30, 25, 21, 19, 17, 15, 13, 11, 9, 7, 5, 3, 1 f/sec.

warning the subject before the presentation of each  
flash rate. Each flash rate being presented for 5  
seconds and separated by periods of 15 seconds, or  
longer if the subject produced massive muscle artefact  
and relaxation was required before any response to IPS  
would be visible in the raw EEG. Following the  
recommendation of Jeavons (1969) the lamp was to be  
switched off immediately any polyspikes or myoclonic  
jerking occurred and then the limits of photosensitivity  
established.

- (h) Enter subject room, record any verbal report of the  
subject on the subjective sensations IPS produced.



- (i) remove grid pattern from the lamp,
- (j) repeat stages d to g.

#### 2.6.6 A check on visual acuity

Part of the experimental method required subjects to focus on the fine grid pattern inserted in the stroboscope 30 cm. from the subject's eyes. In section 1.8 mention was made of work which demonstrated alterations in the VEP with defocusing of pattern, and it is known that due to refractive errors some individuals are unable to focus clearly at 30 cm. distance. Such difficulty would be most likely to occur in the older migraine patients and their matched controls for with increasing age the eye loses some of its power of accommodation. Visual acuity charts (Emsley, 1976) are available. With the aid of the Ophthalmic Optics Department a slide was made of an acuity chart, such that the letters were scaled down for viewing at 30 cm. instead of at the usual distance of 6 metres.

To test a subject's visual acuity the following procedure was employed:

- (a) insert slide, mounted on a clear sheet of perspex,  
in front of the stroboscope,
- (b) give the subject instructions,
- (c) if the subject had glasses to correct refractive  
errors (to enable close vision) they wore them,
- (d) the subject covered one eye with the palm of the hand,
- (e) the experimenter set the stroboscope to maximum  
rate of flash (approx. 70 f/sec.). This rate would  
illuminate the acuity chart and appear as continuous  
light to the subject.

- (f) the subject was asked to look at the lamp and a 5 sec. burst of IPS monitored to ensure no abnormality occurred.
- (g) leaving the stroboscope on the subject was instructed to read the acuity chart from top to bottom as far as they could, the response being noted. The lamp was turned off.
- (h) the procedure was repeated (d to g) for the other eye.

This check on visual acuity proved worthwhile. Firstly, because one student was found to be blind in one eye (the blindness being caused by a childhood accident) and this individual was therefore excluded from analysis. Secondly, because two adult subjects (one migraine patient and one control) failed to reach the criterion set for minimum acceptable visual acuity for this study and were therefore excluded. The criterion was that subjects should be able to read, with each eye, down the chart at least as far as the line which indicates 6/12 vision when the full-size chart is read at 6 metres.

#### 2.6.7 Visual Evoked Potentials

The VEPs were obtained using a Technical Measurement Corporation Computer of Average Transients (CAT), displayed on an oscilloscope and a permanent trace obtained via a Hewlett-Packard X-Y plotter. All VEPs were recorded from two selected channels (see below) and obtained with the CAT set to record at a vertical range of  $10^{3.5}$ ; a sweep time of 0.5 sec. and the number of sweeps in a sample being 25. As the resolution of activity recorded by the CAT is inversely proportional to the sweep duration, i.e. the longer the sweep duration the lower the maximum frequency that can be faithfully recorded, a sweep time of 0.5 sec. was chosen as providing both adequate resolution and a

sample window large enough to include the VEP components of interest, notably any occipital spikes (OS). The sample size of 25 sweeps is the number routinely used in the Neuropsychology Unit in studies of photosensitivity, as this number of sweeps provides a sufficient improvement in the signal to noise ratio to yield a clear VEP in which any OS is readily apparent.

Before recording any VEPs, calibrators (Lindley and Harding, 1974) were inserted into the headbox under the electrode inputs from  $O_1$  and  $O_2$ . These provide a 5 microvolt calibration pulse at the start of each sample. They were used for the first two VEPs recorded which were obtained using the Internal Trigger facility of the CAT. This facility enabled each sweep to have the calibration signal at the start and the strobe flash to occur 50 msec. into the sample sweep so that no overlap of calibration and VEP occurred.

The calibrators were not used during the recording of VEPs to flash rates of 1, 3, 5, 7 and 9 f/sec. as these were obtained using the external trigger facility of the CAT. In this form of triggering the stroboscope output, via a selected EEG channel (Channel 11 in this study, see Fig. 2.12) triggers each new sweep once the previous one is completed. Use of the calibrators in this mode would have contaminated the VEP.

The VEP investigation was carried out as follows:

- (a) recheck CAT and X-Y plotter settings and calibrations
- (b) instruct subject on procedure to be followed
- (c) subjects were tested with their eyes open
- (d) subjects were warned prior to the onset of each train of stimuli

- (e) the montage shown in Fig. 2.12 was used
- (f) the first two VEPs were obtained using the CAT Internal Trigger, with a calibration signal, (see above) with each VEP being obtained from Channels 9 and 10. One VEP being obtained to stimulation with diffuser only and the other with the grid in position, the order of presentation being alternated in each successive subject in each sample (controls receiving them in the same order as the migraine subject they were matched to)
- (g) the remaining VEPs were obtained using the CAT External Trigger. This required one CAT channel to receive input from the EEG channel recording the stroboscope output and this left one channel available for EEG data. In section 1.8 it was noted the dominant hemisphere produces amplitude differences and therefore the VEP was recorded from the dominant hemisphere of the subject (i.e. Channel 9 or 10 as appropriate). These VEPs were obtained to the following stimulus conditions:
  - (i) Diffuser only at 1, 3, 5, 7 and 9 f/sec.
  - (ii) Grid in front of stroboscope diffuser at 1, 3, 5, 7 and 9 f/sec.

The order of presentation of these ten different stimulus conditions was individually randomized for each migrainous subject with their matched control receiving an identical order of presentation. It was hoped this randomization would cause any order effect (fatigue or habituation) to average out on group analysis.

- (h) Throughout each VEP recording the EEG was monitored for any abnormality to IPS. The lamp was to be switched off immediately polyspikes or myoclonic jerks occurred.

The procedure for the patients in the pattern study was identical to that above except that for item (g) above the Internal Trigger continued in use and a series of Normatone patterns (fine vertical lines, fine horizontal lines, fine grid, medium grid, coarse grid, fine checkerboard, fine line spiral, 'fortification spectra' pattern, fine spots) were presented. These will not be described further in this study except to mention that no abnormalities were evoked by any of these patterns (see section 2.7).

After the last VEP the CAT was returned to the Internal Trigger mode, the stroboscope switched off and a biological calibration run obtained from Channels 9 and 10 as a check on any drift in amplitude write-out from the first VEP. No significant drifts occurred.

#### 2.6.8 Final aspects of procedure

After the end of the VEP recordings subjects were transferred from the bed to the low chair and their electrodes removed using acetone. If not already completed the semi-structured interview based on FQ was completed (see section 2.6.2). Subjects wishing to take preventative medication against any possible migraine attack did so.

## 2.7 Analysis of Electrophysiological Data

Once all the EEG recordings had been completed the EEG records were masked, randomized and coded. During the masking process an information sheet was taped over the label giving the subject's name and basic details. The information sheet was filled in to supply only that information required to assess the normality of the basic record, i.e. subject's age and sex, date of a woman subject's last menstrual period, time elapsed since they last ate (and if given glucose drink, see section 2.6), details of any drugs consumed that would affect the EEG activity, the dominance of the subject, any other relevant information, e.g. feels sleepy. The basic record and the responses to IPS were analyzed and the details recorded semi-quantitatively. Once this assessment had been completed for all subjects the EEG data was decoded, united with the clinical data, and further analysed. The author assessed the masked EEGs for unusual or abnormal responses (see below). A random sample (comprising 14% of all the subject EEGs recorded) was independently checked by a consultant electroencephalographer and the level of agreement was 95%. Of the remaining EEGs, any thought abnormal or borderline were referred to the consultant for a second opinion, as were any about which there was any query.

### 2.7.1 The basic records and the hyperventilation response

The records were examined for focal or diffuse slow activity in the theta or delta ranges, paroxysmal activity (spikes, sharp curves, spike and wave complexes, episodic slow waves) and responses to hyperventilation. The incidence of such activity is summarized in Table 2.19 and these are described and discussed below.

TABLE 2.19 Table summarizing abnormal or unusual responses for the age of the individual, in the basic record and in response to hyperventilation.

EEG Feature	Study Groups				
	CM	CC	SM	SC	SF
	n = 45	n = 45	n = 25	n = 31	n = 8
Generalized excess slow	0	1	0	0	0
Focal or lateralized slow activity	0	0	0	1	0
Asymmetry (marked but within normal limits)	3	2	1	1	0
Asymmetry (abnormal)	0	0	0	0	0
Paroxysmal discharge	0	1	1	1	0
Hyperventilation (marked response)	8	5	4	3	1
Hyperventilation (abnormal)	1	0	0	0	0

Generalized excess slow activity was seen in one subject (CC 51), the EEG displaying short runs of 5 c/s. activity in all derivations in the eyes closed condition. During hyperventilation this activity became predominant and K complexes were evoked. The EEG was considered consistent with either extreme drowsiness or narcolepsy. This male individual aged 44 reported that mild, generalized tension headaches occurred two or three times a year and gave an insignificant clinical history.

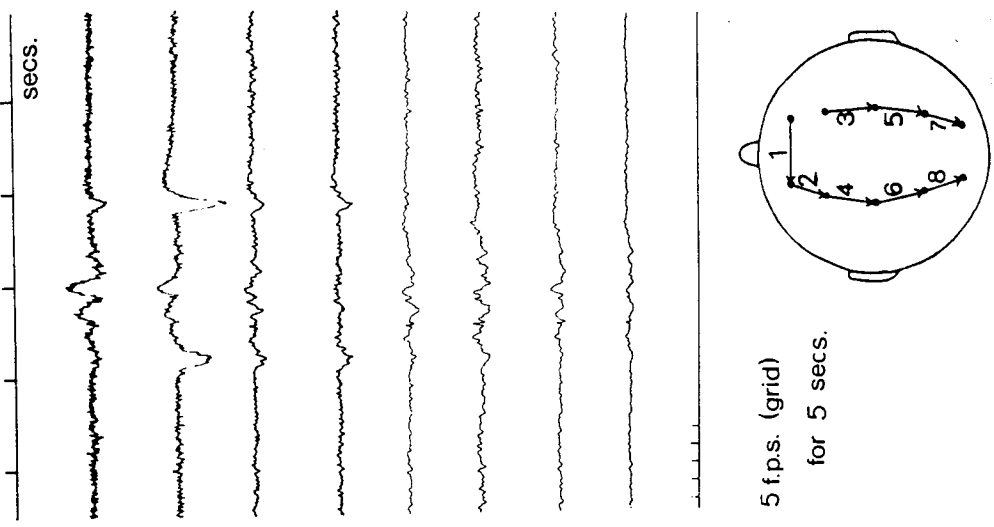
Focal or lateralized slow activity was seen in one subject (SC 172) in whom 4 c/sec. activity was seen in the right posterior quadrant and this became more prominent during hyperventilation and attenuated on eye opening. This 21 year old young woman occasionally had frontal headaches, which were considered non-migrainous, gave no history of head injury and her clinical history was unremarkable. Thus the observed abnormality cannot be related to any specific cause.

No record was sufficiently asymmetrical to be considered abnormal, although a number showed a marked asymmetry of the alpha activity. There was no significant difference in the incidence of such asymmetry in the migrainous as compared with their matched controls. None of the migrainous showing asymmetry had had a migraine in the previous 5 days and none of these reported any loss of motor function accompanying their migraine attacks.

The term paroxysmal discharge was used to cover episodic slow waves. One case thought to have narcolepsy or be excessively drowsy was discussed above. Two of the three cases listed under paroxysmal discharges (CC 31 and SC 129) were both drowsy and exhibited short



runs of theta and these records were considered normal for drowsy persons. The remaining individual (CM 94) showed epileptiform activity in her EEG (see Fig. 2.13). Her EEG was normal prior to hyperventilation, during hyperventilation EMG artefact made assessment of the record for abnormal spikes difficult but after 160 sec. a spike and wave complex is seen. This discharge is most marked in the left central-parietal derivation. Later, about one second after IPS at 5 f/sec. is terminated the eyes were briefly shut, and another spike and wave complex is seen, again being most marked in the left central-parietal derivation. Stimulation with IPS at 5 f/sec. was repeated but no abnormality was seen and it is considered that the abnormality was unrelated to IPS. This abnormal record was obtained on Day 8 of the subject's menstrual cycle, when the EEG was repeated on Day 19 no abnormalities were seen. The young lady described both tension headaches and unilateral headaches, associated with an inability to focus and occasionally associated with nausea. These migrainous type headaches had started when she was aged 16, usually occurred once or twice a month and rarely inconvenienced her. The pain was marked for no more than half an hour, being alleviated by Panadol and was usually followed by a period of depression. They could be preceded by unusual hunger and on one occasion some years previously, had been followed by slight, short-lived, hemiparesis but she could not remember which side was affected. The subject had no personal or family history of epilepsy, no history of head injury and had eaten a meal half an hour before both recordings. As the abnormality was not seen on the repeat EEG the findings would be consistent with a slightly low convulsive threshold at the time of the first recording possibly related to the stage of the menstrual cycle. Neither of the recordings was taken within 14 days of a previous tension or migraine-type headache.



5 f.p.s. (grid)  
for 5 secs.

The EEG of this young woman was generally within normal limits. However, spikes, mainly in the posterior region were seen (see text). This record was taken on Day 8 of the menstrual cycle, a subsequent EEG on Day 19 showed no abnormalities (see text).

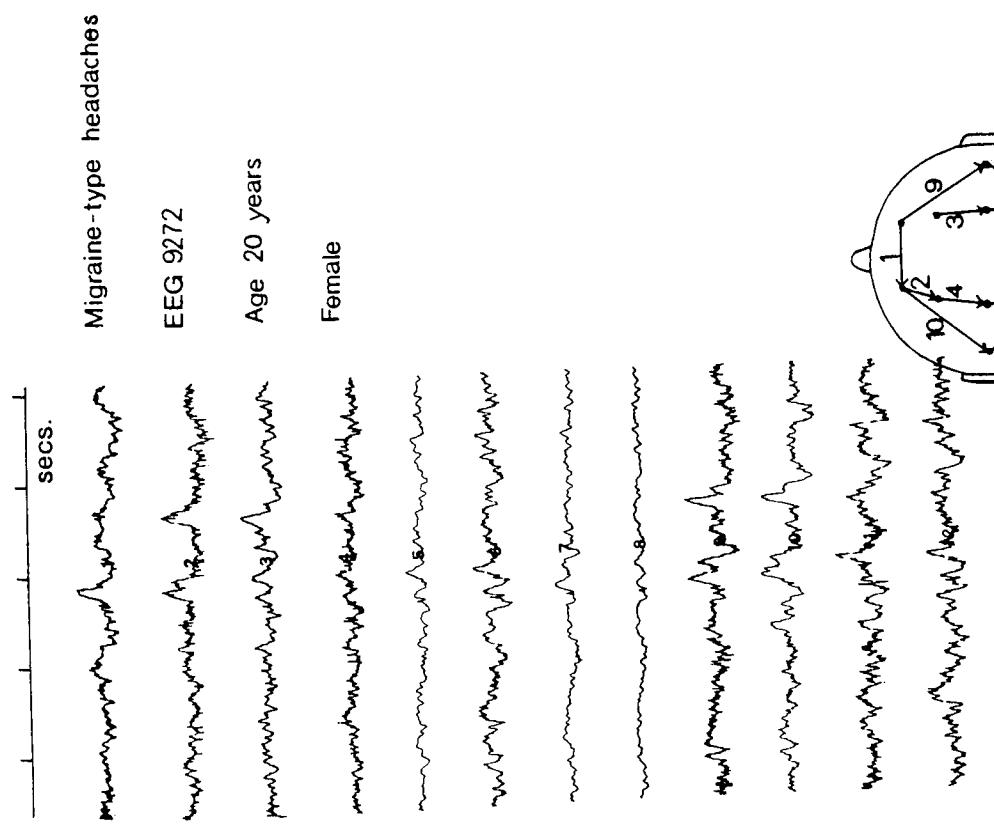


FIG. 2.13

160 secs. after start  
of hyper-ventilation E.C.

Migraine-type headaches

EEG 9272

Age 20 years

Female

A greater number of the migrainous showed a marked response to hyperventilation than did the controls (the difference was not significant) but in only one case was the response beyond normal limits. This 44-year old man (CM 22) had eaten about  $1\frac{1}{2}$  hours before the recording and had had a migraine attack the previous day for which he took one Migril tablet. His headaches were unilateral and incapacitating, they were characteristically preceded by right homonymous hemianopia and paresthesia and were accompanied by photophobia, giddiness and nausea. He had an unremarkable clinical history. The resting EEG record was normal but the response to hyperventilation was marked and abnormal with generalized high amplitude runs of 3 c/sec. activity lasting up to 3 sec. being seen at the end of hyperventilation. The record took two and a half minutes to return to normal, which is excessively long. This marked hyperventilation response could be related to cerebrovascular insufficiency. Such marked responses have been previously observed in the migrainous, as discussed in section 1.10 where it was noted some authors suggest the migrainous may show an exaggerated reaction to hyperventilation. Certainly the results of this study indicate a trend in that direction but the difference (when marked but not abnormal responses are included) was not significant.

To put the results summarized in Table 2.19 in perspective not only should the previous work on the hyperventilation response in migraine be mentioned (see above) but also it should be recalled that in section 1.10 it was noted that in any group of normal individuals 10 to 15 per cent may show some EEG abnormality. In this study 4 individuals (2.6% of all those studied) showed what were considered abnormal records (i.e. CM 22 with abnormal response to hyperventilation;

CC 51 with possible narcolepsy, SM 94 with epileptiform activity and SC 172 with focal slow activity). This number is less than would be expected by chance, and is in part attributable to the deliberate policy of exclusion of subjects with a history of severe head injury, or other complicating conditions, including students or volunteers for the CC group with a history of epilepsy. It is of interest that the clear abnormalities are evenly spread between the migrainous groups and their matched controls. The only trend noticeable in the responses considered marked but within normal limits is that for hyperventilation (see above).

The finding of one individual with epileptiform activity in their EEG record is statistically acceptable on the following grounds. If, as suggested in section 1.9, 0.5 to 0.6 per cent of the population are epileptics then in an unselected group of 154 persons one would expect one epileptic individual. However, this group of 154 subjects was selected insofar as no migraine clinic volunteers or volunteers to be their matched controls had a history of epilepsy but that the student with a history of epilepsy was excluded. In the event, of the 327 students returning questionnaires one woman gave a history of epilepsy ( 0.3%), whereas one would expect two such individuals. Therefore while this finding of epileptiform activity is of interest it cannot be regarded as of statistical significance. In the absence of manifest fits and since no epileptiform discharges were seen at the subsequent recording, the clinical significance was regarded as indicating a low convulsive threshold at the time of the first recording, rather than bearing any direct relationship to the headaches suffered by the subject.

### 2.7.2 Abnormal responses to IPS

When the study records were inspected none of the 154 subjects showed abnormal responses to IPS in their EEG record. However, of the additional 36 normal subjects recorded (rejected controls and pilot runs) one female student did show abnormal responses to IPS (see Fig. 2.14). This 20-year old female had bilateral headaches associated with pain in the neck and shoulders. Her severe headaches were sometimes associated with photophobia and nausea. Waters and O'Connor (1970, 1971) found that of women with headaches accompanied by nausea, only 23.5% would be diagnosed migrainous (see Table 2.2). It is therefore likely this young woman has non-migrainous headache. She has no known personal or family history of epilepsy and no history of head injury. Her basic record showed alpha activity at 11 c/sec. and a little theta activity at 7 c/sec. in the posterior quadrants, this being more marked on the right. Hyperventilation did not affect the theta but slowed the alpha to 8 c/sec. On photic stimulation with the fine grid 15 f/sec. evoked some 4 to 5 c/sec. theta activity after two seconds of stimulation. At 13 f/sec., after 3 seconds of stimulation, a PCR was obtained, with a similar abnormality occurring at 11 f/sec. after a similar amount of time (see Fig. 2.14). Lower flash rates evoked photic driving but no abnormality. With the grid removed no abnormality was evoked (a finding consistent with the studies on PSE by Jeavons and Harding (1975) as discussed in section 1.9.9). The VEPs to both grid plus diffuser and to diffuser only were examined and no occipital spikes were observed. On page 92 of their book Jeavons and Harding (1975) reported a study in which four of the 46 PSE patients investigated did not show occipital spikes. In one of these a PCR was evoked by 1 f/sec. which adversely affected VEP recording but for the other three no explanation was offered for the absence of occipital

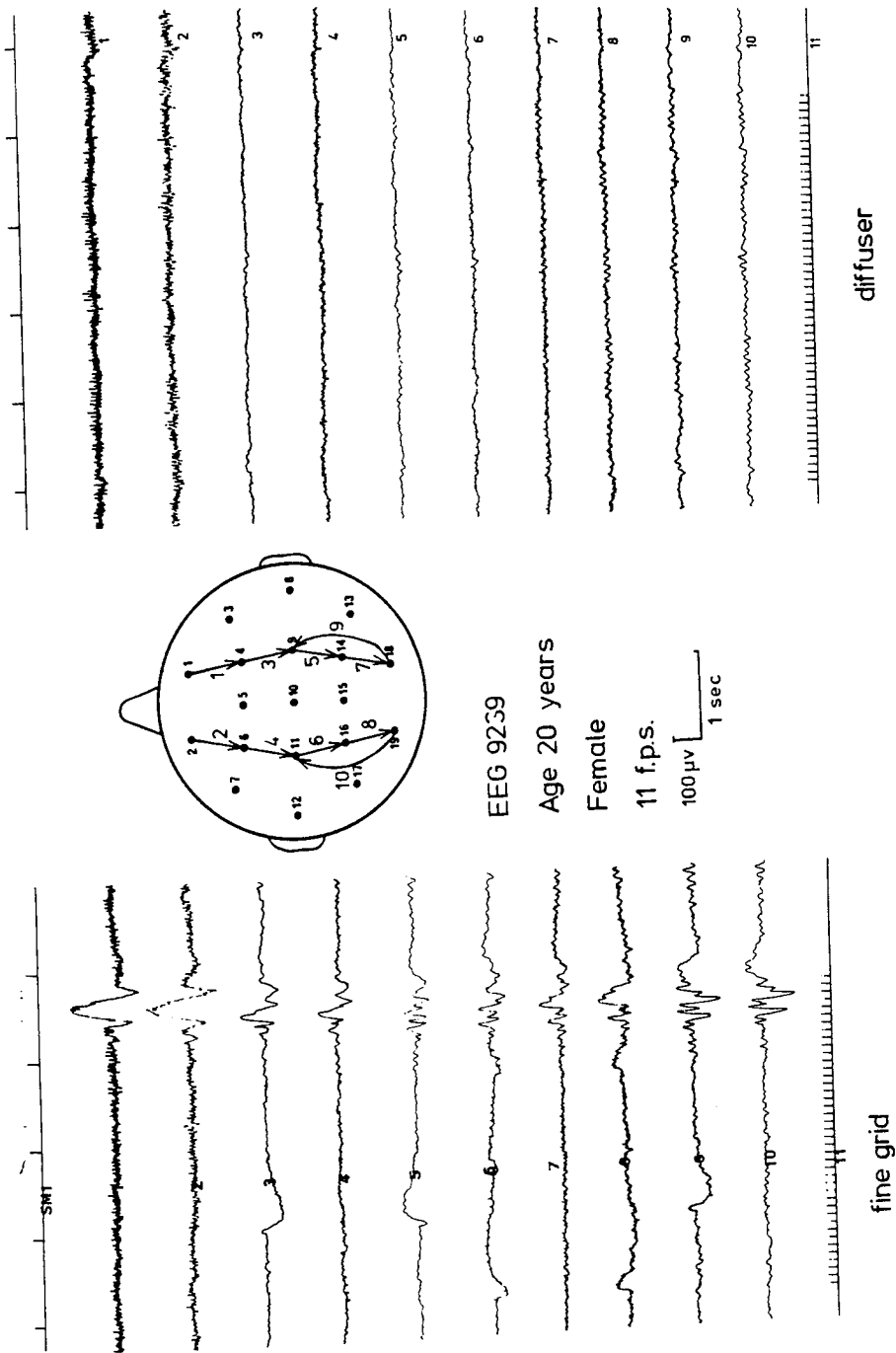


FIG. 2.14. Non-migrainous female subject who assisted with a pilot run for this study. She has no known personal or family history of epilepsy but exhibited a PCR to IPS rates of 11 and 13 f/sec. when the fine grid was placed before the stroboscope. The VEPs were within normal limits for the age and showed no occipital spikes (see text).

spikes, although it was noted all three produced an absence with bilateral 3 c/sec. spike and wave activity to IPS. This individual did not show such activity. The subject was closely questioned regarding her subjective sensations during IPS and reported they did not affect her. No behavioural change was observed during any of the abnormal responses. To put this case in perspective, Jeavons (1969) writes:

"A photoconvulsive response does not necessarily indicate the patient has photosensitive epilepsy ....."

and Jeavons and Harding (1975) write:

"Photoconvulsive responses may be found in the symptom-free siblings of children with photo-sensitive epilepsy, and very rarely in normal subjects. This latter finding indicates photosensitivity to the massive, provocative stimulus used in the laboratory and it is entirely possible that the individual may never encounter such a powerful stimulus in the outside world." p. 107.

Thus this young woman may be regarded as exhibiting laboratory sensitivity to IPS and in the absence of clinical fits would not be regarded as epileptic (see section 1.9) but as exhibiting a slightly lower convulsive threshold than normal.

In section 2.7.1 one female student with paroxysmal activity in the basic record was discussed. If she and the young woman excluded from the study by manifest epilepsy are added to the individual discussed here, three students of the 327 returning questionnaires are now known to have epilepsy or epileptiform EEG activity. This new observed incidence remains not significantly different from the expected incidence. These findings are further discussed in Section 3.

### 2.7.3 Occipital spikes in the VEPs

None of the subjects in the study groups exhibited evidence of occipital spikes in their VEPs. This is discussed in Section 3.

### 2.7.4 Examination of the EEGs for photic driving

Visual inspection of the masked EEGs revealed considerable variation in both the range of flash rates to which photic driving (PD) could be seen and in the amplitude of those responses to any one flash rate. In the absence of automated frequency analysis some form of quantitative analysis was required before any comparisons between the migrainous and their controls could be effected.

Initially an adaptation of the rating method used by Bille (1962), and described in section 1.10, was contemplated. The method and the results of a check on its reliability are described below. A series of identical rating sheets were prepared, these started with a definition of PD as follows:

"Waves occurring at the same frequency as the photic stimuli are known as fundamentals. The driving of harmonic and sub-harmonic rhythms may also be observed. They are defined as follows:

fundamental	-	$f$	
harmonics	-	$m \times f$	$m = 2, 3, 4 \dots n$
sub-harmonic	-	$\frac{1}{m} \times f$	$m = 2, 3, 4 \dots n$ "

An example of fundamental, harmonic and subharmonic rates calculated from a particular flash rate given and then the modified ratings of Bille (1962) followed by the instructions to raters (see below). The rating method used by Bille (1962) used only verbal terms (see page 178) and was used to rate the responses to IPS of about 15 f/sec. and over as a group. In this study the rating method was used separately for each individual flash rate and numerical guidelines were added with



the intention of making the assessments less open to varying interpretation.

"0 = ABSENT, i.e. basic pattern (of EEG) not influenced at all

1 = RARE, i.e. rare or sporadic photic driving (0 to 1/3 of period)

2 = OFTEN, i.e. fairly pronounced photic driving (1/3 to 2/3 of period)

3 = CONSTANT, i.e. constant throughout IPS (2/3 plus of period)"

### Instructions to raters

Please circle the appropriate rating code (see above) for degree of photic driving at each rate of IPS.

### Example:-

#### IPS at 40 f/sec.

Fundamental	0	1	2	3
1st harmonic	0	1	2	3
1st subharmonic	0	1	2	3

Note: Any additional comments by the raters on the photic driving will be welcomed, e.g. if at slow rates of IPS one observes especially prominent evoked potentials in the EEG rather than photic driving."

No cut-off on the flash rates for those evoking PD as opposed to VEPs was given as the literature (see section 1.8) puts this rather vaguely at around 5 to 7 f/sec., presumably because of variation in the responses produced by different subjects.

With the aim of further reducing variability between the raters, each rater was provided with a transparent overlay giving the stroboscope output at different flash rates (see Appendix 4). The idea for producing this overlay was derived from the description by Sulg (1969) of the transparent plastic 'multiscale for period analysis' he developed

as an aid for manual EEG analysis. It was hoped this would especially aid the raters in assessing the responses to faster flash rates, and in assessing harmonics which are not always easy to distinguish from the 'noise' of underlying EEG activity, including muscle artefact.

Using the rating sheets and the overlays three independent observers (the author and two full-time members of staff of the Neuropsychology Unit) assessed the first twenty-five of the coded EEGs for PD to IPS in both the grid and diffuser and diffuser only conditions. To assess the inter-rater reliability three rates of IPS were arbitrarily selected as follows, 7 f/sec. because it was at the lower end of the spectrum where marked VEPs rather than PD might be seen; 19 f/sec. as being in the region where an extended range of PD would be seen and 13 f/sec. as being midway between these two. Consultation of Kirk (1968) and Holsti (1969) indicated the most suitable test for the data as being Scott's 'pi' test. The widely used coefficient of reliability in the ratio of coding agreements to the total number of coding decisions and Scott's 'pi' corrects this not only for the number of categories in the category set, but also for the probable frequency with which each is used. The results of these tests are shown in Table 2.20 for fundamental and harmonic PD, these being the types of driving previously considered in relation to migraine (see section 1.10). As can be seen from Table 2.20 the agreement between the rates was not high enough to justify the use of this rating method.

The ratings and the original records were re-examined with the aim of identifying possible sources of error that could be better controlled on re-analysis. On visual examination it was apparent that the three raters tended to agree totally or else two raters agreed and the third

TABLE 2.20

Table showing results of test of inter-rater reliability of 3 raters using the rating method described in the text to assess photic driving in response to IPS with grid (G), with diffuser (D), or to the combined results for each flash rate (G & D).

Category type and IPS rate			Coefficient of reliability			Scott's 'pi'		
			G	D	G & D	G	D	G & D
Fundamental to 19 f/sec.			0.42	0.32	0.37	0.36	0.26	0.32
"	13	"	0.33	0.23	0.28	0.33	0.23	0.24
"	7	"	0.50	0.50	0.50	0.50	0.17	0.42
1st Harmonic to 19 "			0.67	0.68	0.67	0.09	0.06	0.09
"	13	"	0.63	0.59	0.61	0.63	0.36	0.41
"	7	"	0.46	0.41	0.43	0.46	0.41	0.14

was one category different. This suggested there was substantial agreement but a need for calculating the proportion of time that the photic driving appears in a more exact fashion. At the time of EEG recording each rate of IPS had been presented for approximately 5 seconds, being given manually the timing was not exact and therefore it was decided to examine the first 4 seconds of each stimulation. Using the overlay each 4 second period would be examined, with periods containing fundamental and periods containing harmonic driving responses being individually marked and their percentage time of occurrence to that flash rate calculated and recorded.

Further confusion arose in the assessment of responses to IPS at 7 f/sec. Some individuals show no visible response and there was no disagreement regarding their ratings. Equally there was no disagreement regarding those individuals showing a clear underlying sinusoidal response. The difficulty arose with individuals showing what might be better described as clear VEPs rather than sinusoidal photic driving. Frequently background EEG activity, especially muscle artefact, made the distinction between these two types of responses difficult. In section 1.8 it was illustrated how when discrete VEPs are overlapped, by increasing rates of IPS, they take the sinusoidal form of photic driving (see Fig. 1.4c), therefore to create an arbitrary distinction between VEPs and PD to 7 f/sec. when they may be judged to lie on a continuum, seemed a fruitless task for the purposes of this study, particularly as the H response involves an extension of photic driving at the higher rates of flash and not the lower rates. Therefore it was decided to accept any clear response at the same rate as the flash whether it appeared sinusoidal or as a series of VEPs.

At the higher flash rates the raters appeared to have problems with background activity. Background activity may include regular activity which matches one of the rates of IPS used (or be a harmonic or sub-harmonic of it). A decision rule was therefore needed for such EEGs to determine when photic driving may be accepted as present.

Suggested Decision Rule: If there is no clear difference between the frequency (c/sec.) of activity occurring during IPS and the background activity occurring before stimulation (see 'a' below), and the activity is at the same rate (or a harmonic or sub-harmonic) of the rate of IPS, then photic driving (whether it be a fundamental, harmonic or sub-harmonic component under consideration) is to be regarded as present only when a clear increase (see 'b' below) in amplitude of that activity occurs during IPS.

Note (a) The activity before IPS stimulation should be examined, to avoid any 'after-discharge' of any sort including continuation or resolution of PD activity that may occur immediately after the cessation of IPS.

(b) A 'clear increase' needs to be quantified. To define it in terms of microvolts, e.g. 10 microvolts creates problems, for at flash rates in the alpha range high amplitude activity tends to be evoked, but at high IPS rates even the most marked PD is of lower amplitude and a 10 microvolts criterion might require a large percentage increase of amplitude. It was therefore decided to arbitrarily define a 'clear increase' of amplitude as an increase of not less than 10% of the amplitude of the background activity.

On examining the sample of 25 EEGs it was clear some had much higher amplitude PD than others and it was wondered whether these individuals would be the migrainous and if this amplitude factor would account for the clear photic driving previous authors had mentioned. To obtain an amplitude measure high accuracy calipers were used to measure the peak to peak amplitude of the fundamental or harmonic components of PD at the point they reached a maximum.

To further define what was to be measured, all measurements were to be taken from the occipital to central derivations in the non-dominant hemisphere. These derivations were those in which PD could be most clearly seen and the non-dominant hemisphere was chosen on the same grounds that this was used for the VEP recordings (see section 1.8).

Thus the records for each matched pair of subjects were finally assessed for photic driving by the method summarized below

1. Mark off the first 4 seconds of each response to IPS in the occipital-parietal derivation from the non-dominant hemisphere.
2. Using the overlay, and operating the two decision rules outlined above for slow flash rate responses and distinguishing PD from background activity at the same rate as the IPS, calculate and record the percentage time that fundamental PD occurs and that harmonic PD occurs to every flash rate.
3. Using the calipers calculate and record the corresponding peak to peak maximum amplitudes.

This data was then united with the clinical data. On visual inspection no clear distinction could be made between the migrainous and their controls on the basis of presence or absence of PD at

higher rates of IPS. It was therefore decided to test whether the migrainous tended to show PD of higher amplitude and occurring for greater percentage of time. In order to do this a series of chi-square tables (one for each IPS condition) were generated. One of the chi-square dimensions was the subject groups (CM, CC, SM, SC, SF), the other dimension was derived as follows. Firstly the scores for percentage time were divided into 5 groups (0%; 1 to 25%; 26 to 50%; 51 to 75%; 76 to 100%). Secondly, where PD was present the amplitude scores were divided into high and low scores. Since the PD to IPS rates in the alpha range is higher than at other rates, scores were divided into high and low not by a single criterion microvolt measure, but by calculating the median amplitude value of the PD to each IPS rate for the population studied and using these to determine high and low values. The median was chosen as the measure of central tendency as this always divided the population into two and so not only created fewer problems for chi-square analysis (i.e. empty cells), but also was not unduly influenced by the few extreme measurements, as the arithmetic mean would be. Thus the second dimension of the chi-squared tables contained nine variable groups (zero response; 1 to 25% of time at low amplitude; 26 to 50% of time at low amplitude; ..... 76 to 100% of time at high amplitude).

The abundance measure used by Golla and Winter (1959) and Smyth and Winter (1964) was essentially a combination of the dimension of percentage time and amplitude. Therefore if their observations of the H response being characteristic of migraine hold true, and the majority of normals show the N response (see section 1.10 and Fig.1.7) then the following predictions for the chi-square analysis should hold true

- (a) At IPS rates in the alpha range there will be no significant difference.
- (b) At 15 f/sec. onwards the migrainous should continue to show high percentage time, high amplitude responses whereas the majority of controls should show zero responses, or ones with low percentage time and low amplitude.
- (c) If a considerable number of control subjects show an A response then a significant difference may be seen only at 15 and 17 f/sec. and at 25 and 30 f/sec.

The chi-square analyses were carried out on a computer and the probability values for the obtained chi-square tables are shown in Table 2.21. As predicted no significant difference is seen at rates of IPS below 15 f/sec. However, the pattern of probability values at higher flash rates is not as predicted. When all groups were compared a significant difference in the distributions did not emerge at any IPS rate to diffuser only (the mode of presentation thought to be used by previous authors), and the only rate showing a significant difference to stimulation with grid was at 17 f/sec. Referring to Fig. 1.7, it can be seen that Golla and Winter (1959) found an A type response to have a trough in the region of 16 f/sec. Thus the results obtained could indicate a high proportion of A types in the control groups, which would obscure the expected differences at higher IPS rates that a division between N and H types would show.

Further analysis to directly compare the CM group with the CC group, and the SM with the SC group, was also carried out (see Table 2.21).



TABLE 2.21 Table showing the probability values for the obtained chi-square tables.

		Groups Compared		
Category Type and IPS (f/sec.)		All Groups	CM cf CC	SM cf SC
Grid	1	.45	.73	.10
	3	.59	.47	.37
	5	.57	.60	.84
	7	.53	.40	.20
	9	.77	.52	.63
	11	.51	.46	.84
	13	.39	.68	.41
	15	.85	.39	.54
	17	.01 *	.56	.05 *
	19	.39	.35	.48
	21	.53	.05 *	.84
	25	.11	.48	.17
	30	.24	.69	.03 *
Diffuser	1	.40	.52	.24
	3	.20	.47	.60
	5	.16	.69	.14
	7	.45	.39	.40
	9	.51	.89	.34
	11	.16	.47	.33
	13	.32	.95	.95
	15	.58	.85	.62
	17	.81	.72	.81
	19	.16	.39	.06
	21	.20	.43	.39
	25	.69	.63	.90
	20	.37	.84	.21

\*significant differences

Again no significant differences to diffuser only were found. The responses to grid stimulation showed the only significant difference between the CM and CC group to be at 21 f/sec., an unexpected finding. In contrast the comparison of the SM and SC groups showed significant differences at 17 f/sec. and 30 f/sec. which would be consistent with a comparison of predominantly A types with predominantly H types.

To follow this up further, the IPS analysis data was re-examined and using, in a modified form, the ratio value calculations of Golla and Winter (1959) it was determined whether each record was an N, A or H type. The original ratio value formulae are given in the legend to Fig. 1.7. Golla and Winter used stimulation rates that were all a multiple of two, whereas this study used mainly odd numbers. Therefore the value for 's' was taken at 19 f/sec. instead of 18 f/sec, 'r' remained the maximum abundance in the alpha range and 't' the lowest abundance between 19 f/sec. and the alpha range. In the absence of automated analysis approximate abundance values in a subject were obtained by calculating the product of the value for total percentage time of PD and its maximum amplitude, to each IPS category. The results of these calculations are given in Table 2.22. The apparently high percentage incidence of the H response may be partly a function of the small number of headache free students in that sample. Comparisons of each migraine group with its matched control group indicated there was no significant difference in the incidence of the H type response in either the grid or the diffuser condition, in variance to the reports by Smyth and Winter (1964) and Townsend (1967). Alternative explanations of the H response, rather than it being specifically associated with migraine or head injury, are considered in Section 3.

TABLE 2.22

Using the modified ratio value calculations (see text) of Golla and Winter (1959) to determine N, A and H type responses, the percentage of records showing those responses in each subject group was calculated, and these are tabulated below.

Stimulus	Group	% in each response group		
		N	A	H
<u>Grid</u>	CM	53	25	22
	CC	62	9	29
	SM	55	13	32
	SC	55	20	25
	SF	37	13	50
<u>Diffuser</u>	CM	26	6	68
	CC	24	16	60
	SM	27	28	44
	SC	37	17	46
	SF	13	0	87

### 2.7.5 Further examination of the VEPs

A visual examination of the VEPs not only revealed no occipital spikes in the study groups but also indicated no responses to be beyond normal limits and suggested there were no differences in latencies and amplitudes between the groups. The latencies of the main VEP peaks and their peak to peak amplitudes were calculated with the aid of the calibration signals obtained at the time of recording. This data was then tabulated for each group and on inspection considerable overlap between the groups was obvious, to an extent that it was decided not to carry out further statistical analysis. In the light of the earlier discussion on the pathophysiology of migraine and the confused findings of earlier studies on VEPs in migraine, it is suggested that more work on a possible relationship between platelet MAO levels and VEPs needs to be carried out. If such work establishes a consistent relationship between platelet MAO and VEPs then it would be of interest to see if the migrainous show a trend towards lower MAO and the associated VEP changes. Conversely, it may be that the VEP configuration may alter not with the MAO levels as such, but in relation to monoamine levels per se. As the migrainous show fluctuations in monoamine levels in the blood, related to the occurrence of attacks, it might be relevant to check monoamine levels and to determine not only when the subject's last migraine attack was (it was also useful to know if there were any persisting features which would affect the VEP, see section 1.10), but also when the next one occurs, and what the subject's usual levels of monamines are.

### 2.7.6 Subjective reports

In this study of VIM it would have been of interest to have none of the subjects taking medication to prevent or abort a possible attack occurring as a result of the IPS stimulation and to record how many suffered a migraine in the 24 hours immediately following their test. There were a number of drawbacks to this suggestion. Firstly, the ethical considerations of inflicting what could be considerable pain each migrainous patient or subject. Secondly, the Neuropsychology Unit operates as an out-patient clinic, and therefore subjects needed to be in a fit state to make their own way home. Therefore, because of both these aspects subjects were given the opportunity to take appropriate medication. Thirdly, a number of patients indicated their susceptibility varied, e.g. woman who were more sensitive to light stimulation when premenstrual and some subjects were more prone when anxious, thus absence of an attack following the test, would not necessarily indicate the patients did not at times have visually induced migraine.

However, a record was made of patients' subjective reports at the time of the recording. Six patients admitted to nausea at this time and of these, two are known to have had a migraine in the following 24 hours, but no specific follow-up was made so the true figures for subsequent migraine remain unknown. Two of the control subjects (CC group) reported a NMH before they left the Unit. Of the students, none of the SM group reported any adverse feelings during the study although one of the SM group is known to have had a migraine in the following 24 hours. Again no specific follow-up was made.

Bille (1962) was the only previous author found to have consistently recorded and reported the subjective responses of migraine subjects to IPS. Of the 73 children with pronounced migraine and the 73 control children that he studied, about 45% were found in each group to report feelings of nausea, giddiness or other discomfort during IPS. However he found significantly more ( $p < 0.05$ ) of the migraine group (15%) than the controls (4%) reported headache during the recording. In addition, if headaches on the way home or on arrival home were included, the difference became highly significant ( $p < 0.001$ ) with 22 migraine children as opposed to 5 migraine children having headache. The incidence of reports of nausea or headache during this study was lower than in Bille's study, whether this indicates a lower susceptibility in adults or a greater reluctance to report such sensations is unclear. The latter is a possibility as subjects were not closely questioned on this aspect. Finally, Bille found no children had an attack of migraine during the EEG but 6 migraine children had attacks after the EEG investigation, either on the way home or immediately on arrival home. Thus it appears IPS can be shortly followed by migraine and that it was a justified precaution for the adult subjects to take medication if they desired before making their unaccompanied journey home.

### SECTION 3

#### DISCUSSION AND SUGGESTIONS FOR FURTHER RESEARCH

### 3. Discussion and Suggestions for Further Research

This section does not seek to repeat in detail the individual points discussed in sections 1 and 2 but rather to:

- (a) integrate these and consider them as a whole in relation to the original questions, and
- (b) consider the implications for further research.

The questions this study originally asked could be summarized as:

- (a) Do people with VIM closely resemble PSE patients or are they distinctly different?
- (b) Do people with VIM show a clear difference from non-migrainous controls?

In the course of the literature review it became apparent that over the years there has been much variation in the definitions of migraine, indeed certain questions of differential diagnosis continue to be raised (section 1.2). A major source of difficulty in arriving at a universally acceptable definition and set of diagnostic criteria arises from the wide variety of symptoms that may precede, accompany or follow migraine attacks (section 1.4). The need for the explicit use of set diagnostic criteria in scientific research, as opposed to the need in clinical practice to consider atypical cases and so arrive at an appropriate diagnosis for effective treatment, was considered in section 1.3. A further review of the literature indicated migraine occurs more commonly in the population than the 5 to 10% often quoted in the literature. The recent work by Prof. Waters in this country is supported by independent findings abroad (see section 1.5) and he suggests (Waters, 1974a) that the population incidence may be as high as 24 to 29% in women and 15 to 20% in men. The large discrepancy between the population values and the earlier sample estimates of



these values, are attributable to the bias in the samples, these being predominantly patients consulting doctors and it has been demonstrated that the majority of migraine sufferers rarely (if ever) consult their doctor (Waters and O'Connor, 1970). It was wondered whether such individuals recognize their headaches as migrainous. Thus it was considered essential that a set of diagnostic criteria be employed not only to ensure that all migrainous subjects satisfied those criteria, but also, especially in view of the high proportion of migraine in the population (which may not be recognised as such by the individuals themselves), that the criteria be applied to exclude from the control subjects those likely to be migrainous. It is suggested all further scientific research on migraine should rigorously apply diagnostic criteria to both experimental and control groups.

The operational criteria used in this study for preliminary selection were the three features of unilateral headache, pre-headache warning symptoms and nausea or vomiting, which were those used by Prof. Waters. These formed the basis of his Headache Questionnaire (HQ1), which had the additional advantage of being a clinically validated postal questionnaire (section 2.1). This questionnaire was therefore used with confidence in this study for preliminary selection of subjects (section 2.2). This confidence was justified in that it provided a good foundation for this study, however it questioned people only about their headaches in the previous year. As it was wished to exclude from the control groups those with a previous history of migraine and those with possible atypical migraine, a supplementary questionnaire (HQ2) was formulated following a review of the literature (section 2.1) and used as described (section 2.2).

From the literature review it was found that migraine is unrelated to intelligence and social class (section 1.5) and therefore these factors did not need to be controlled. However the incidence of migraine is higher in women than men so this was taken into account when obtaining the student samples (section 2.2). Moreover, because of the effect of the age and the sex of the subject on EEG and VEP recordings (section 1.8), the controls for the migrainous subjects were individually age and sex-matched (section 2.2). In addition care was taken at each stage of the study to exclude people who suffered certain other conditions which might unnecessarily complicate the interpretation of results. These conditions (mentioned in section 2.2 and elsewhere, see below) included:

- (a) any known loss of visual field due to retinal or brain lesion (see section 1.4.6 regarding persisting and permanent deficits resulting from migraine);
- (b) inadequate visual acuity when focusing at 30 cm. (see section 1.8 on pattern VEPs and section 2.6 for method of testing);
- (c) a history of severe head injury. The consequence of head injury may include headaches, and if brain damage was caused by the injury, symptomatic epilepsy may result (section 1.9). The suggestion of a direct relationship between migraine and epilepsy was an item of interest and thus head injury and its possible complications regarding the advent of observed headaches or epilepsy had to be excluded.

So far this discussion has aimed to demonstrate that considerable care was taken in the selection of subjects for study, and it is to be hoped that future studies will also exercise careful control of variables.

However the control of variables in this study was not entirely adequate, as will be discussed later in this section.

In addition to the selection processes outlined above the patients from the Migraine Clinic (CM group) were initially selected on the basis that their migraine could be visually induced by bright light or flicker. In order to ensure the subjects genuinely believed (and acted accordingly) that they had visually induced migraine (VIM), a semi-structured interview was carried out. The basis of this interview was the 'Flicker Questionnaire' (FQ) developed from the literature review of photosensitive epilepsy (PSE) and of migraine, and from early interviews at the Migraine Clinic (sections 2.1 and 2.2). This form of interview was deliberately chosen with the aim of obtaining relevant information with the minimum of suggestion regarding the type of answers expected by the interviewer. A formal paper and pencil test would not have uncovered precipitants not previously reported in the literature on migraine (see below) and might have encouraged false positives. Before discussing precipitants of VIM and/or PSE consideration will be given to the wider question of a relationship between migraine and epilepsy.

The literature on a possible relationship between migraine and epilepsy was critically discussed in section 1.9, after considering briefly the definition and classification of epilepsy. That discussion will not be repeated here. The reader is referred to page 129 where a number of important questions were raised, and to pages 130 to 147 where an attempt to answer them is made. It was concluded that studies suggesting a close relationship between migraine and epilepsy are open to question on one or more of the following counts:

- (a) inadequate definitions
- (b) problems of differential diagnosis
- (c) inappropriate criteria for EEG activity indicating epilepsy
- (d) bias in the samples studied

It is worth repeating certain conclusions and comments here.

"For there to be a genetic relationship two conditions should hold. Firstly migraine should occur in epileptics more often than by chance, which in the light of modern population estimates for migraine prevalence, was shown not to occur. Secondly, epilepsy should occur more often than by chance in the migrainous and no clear bias has been shown. Thus one can assume there is no simple genetic linkage but one cannot necessarily assume that the migrainous are not at greater risk of epilepsy than the general population."

Consideration was given to two possibilities, firstly that severe migraine may cause symptomatic epilepsy, and secondly that vasoactive substances implicated in migraine may alter convulsive thresholds.

It is suggested the finding that tyramine activates the EEG (Moffett, Swash and Scott, 1972; Scott, Moffett and Swash, 1972; Moffett, Swash and Scott, 1974b) but not chocolate (Moffett, Swash and Scott, 1974a) should be verified by further research. This, and a number of other suggestions arising from the literature review in section 1.9, is included in the list of suggestions for further research below.

In view of the discussion in section 1.9 the finding, reported in section 2.4.2, that 5 (1.4%) of the patients attending the Migraine Clinic in the study period reported a history of epilepsy, as compared to a population incidence of epilepsy of 0.5 to 0.6%, was considered not necessarily to indicate any genetic connection. To clarify the question of any relationship between migraine and epilepsy generally, studies on representative samples of the migrainous, and not highly selected patients, needs to be made. A point which also emerged in

in section 1.10 when considering EEG characteristics of migraine.

The literature on PSE (section 1.9.9) was originally examined with two aims in mind, firstly to extract a list of visual stimuli that will precipitate PSE and, secondly, to establish the EEG and VEP characteristics of PSE so that the recordings obtained from the VIM patients could be examined for these. An initial table was prepared (Table 1.8, page 153) comparing the types of visual stimuli reported in the literature as precipitating PSE and/or VIM and a considerable amount of overlap was apparent on visual inspection. The semi-structured interview using FQ concentrated on common situations precipitating PSE and/or VIM but gave the opportunity for additional comments to be made and recorded. As a result, the reports from both the CM and SM groups enabled Table 1.8 to be expanded, as shown in Table 2.17 (page 266). Some of this expansion rounds out certain groups of features already identified, for example, a low sun directly ahead (which especially affected car travellers) can be grouped with 'bright sunlight itself'. Similarly travelling past bridge or tunnel columns (as at massive motorway junctions including Birmingham's 'Spaghetti Junction'), is a new variant on travelling past trees or railings. However, certain additions are of previously unreported groups of features producing glare or flicker in the environment. Firstly the adverse effect of certain modes of lighting in vehicular tunnels does not appear to have reported outside the pilot study for this thesis (Debney, 1973). Secondly, the hazards of night driving, i.e. headlights (both oncoming and reflected in the driver's mirror), and the brake lights or flashing indicators of the car in front, seem to be previously unrecognized except in the case-history of West (1975). In addition, the little reported effect of patterns in inducing

migraine was substantiated, with 20 of the 45 patients in the CM group reporting patterns could provoke a migraine and a further 4 patients of the 13 interviewed but not tested also reporting this. The importance of such observations in relation to work in the visual system by workers including Hubel and Wiesel was mentioned and, of particular interest here, the effect of pattern in enhancing sensitivity to IPS in photo-sensitive epileptics (section 1.9.9). Finally, in section 2.5 it was shown that a number of migrainous subjects considered certain colours, notably a bright red, could precipitate migraine attacks. This was an unexpected finding and it is believed that this has not previously been reported in the literature. The significance of this finding lies not so much in its absence in previous reports on migraine, but in the presence of reports on PSE that certain colours of light (e.g. white or red) are more effective in precipitating fits than certain other colours of light (i.e. blue). Thus initial findings suggested close similarity between PSE and VIM.

However on further analysis in section 2.5 and illustrated in Fig. 2.10 it was clearly demonstrated that the apparent similarity seen in Table 2.17 is only superficial, for the proportion of patients affected by any of the groups of precipitant factors was very different in the two conditions (i.e. PSE and VIM). Why this should be so is a matter for further research. It would also be of interest to uncover why PSE affects only a small proportion of epileptics (0.5% of epileptics was a figure uncovered in the literature review), whereas a substantial proportion of the migrainous may be regarded as having VIM, all previous reports on the percentage of the migrainous affected by visual stimuli are higher (see Table 1.4) being about 24% to 84%. This study found 58% of the men and 67% of the women attending the Migraine Clinic had

visual precipitants noted in their medical records (the disadvantages of medical records as sources of information being discussed in section 1.5), and 84% of the SM group to have migraine induced by visual stimuli.

The theme of apparent similarity being superficial continued to be seen in other findings. Firstly, the effect of lateral flickering illumination of car drivers and passengers was compared (section 2.5) and it was concluded that lateral illumination from a flickering source can induce VIM, which implies involvement of the peripheral part of the retina, whereas reports in the literature (Jeavons and Harding, 1975) indicate macular illumination appears essential to precipitate PSE. The implications of such findings are beyond the scope of this study to discuss in any detail. It is asked whether the effect in VIM of lateral illumination lies either in its effect on pineal melatonin and thus brain serotonin levels (see section 1.7) or by some other pathway as a generally arousing stimulus?

The pattern of superficial similarity but significant difference was also seen when the distributions for the age of onset of VIM and PSE were compared (Fig. 2.3 and 2.5) in pages 232 to 236. The distribution for VIM patients at the Migraine Clinic conformed to that expected from the literature review (section 1.5) and as a whole was not significantly different from non-VIM patients attending the Migraine Clinic during the study period. However it was significantly different from the distribution of PSE ( $p < 0.001$ ) for while VIM and PSE had similar ranges for age of onset and similar modes (i.e. in the age group 10 to 15 years) the VIM distribution was wide (rather than narrow) and had a marked positive skew. It was suggested this indicated

the two patient groups do not come from the same population, even though influences, perhaps hormonal, at the age of puberty play a role in precipitating the first identifiable attacks in both conditions. The role of female hormones in migraine (see section 1.6) may help produce the predominance of female migraine sufferers, the literature in section 1.5 suggesting a female to male ratio of 3:2. The ratio of males to females with VIM was found to be close to this at 3.3:2 (section 2.4). It was noted that while males tend to predominate in the general epileptic population, PSE shows a female to male ratio of 3:2 (Jeavons and Harding, 1975). Therefore, in section 2.4, while a discussion on why females should be more susceptible to PSE, was outside the scope of this study, a comparison of biochemical abnormalities known to occur in PSE, with those discovered in migraine might more firmly establish why those with PSE and those with VIM show certain similarities and yet are different.

At this point any similarity between PSE and VIM ceases for none of the migrainous showed any of the photoconvulsive responses (section 1.9.9) characteristic of PSE and none of them exhibited any occipital spikes in their VEPs, a frequent finding in PSE. However, one subject with NMH who acted as a subject in one of the pilot runs did show PCRs but not any occipital spikes in the VEP. The clinical significance of this finding was discussed in section 2.7. It is recognised that a small percentage of normal subjects, this young woman had no clinical history of epilepsy, will exhibit an abnormal response to the massive stimulus provided under laboratory testing conditions. Therefore this finding is of interest but should not be regarded as untoward or of any significance to the question under study. That question was to establish if there were evidence supporting an association between VIM



and PSE. From the above overview of preceeding, more detailed, discussions the conclusions that emerge can be summarized as:

- (a) No fundamental similarity in terms of electrical brain activity evoked by IPS exists between PSE and VIM.
- (b) Despite superficial similarities between VIM and PSE in terms of the types of stimuli that may provoke PSE and/or VIM; and the distribution of the age of onset of the conditions, there are seen to be significant differences between the two groups on a closer examination of these factors.
- (c) The list of visual factors known to precipitate VIM has been enlarged. The addition of colour (notably red) was unexpected, and is thought not to have been previously reported in the literature.

Finally, this study has not sought to consider particular therapies for VIM, although some mention was made of suggestions in the literature (section 1.6.10). Whether or not VIM and PSE are closely related as regards underlying mechanisms, there is a possibility the migrainous may benefit from an idea originally formulated to aid those with PSE. Jeavons and Harding (1975) describe special glasses intended to protect the wearer from excessive light input and from flicker. One feature was the lenses which were composed of three layers. Firstly an ordinary lens which could be prescribed to correct any refractive errors, secondly a polarizing layer to cut-out environmental glare and thirdly, a photochromatic layer which adjusts to different lighting levels and protects the eye from high input of light. If not already tested in the migrainous it is suggested such

glasses may prove particularly useful to them and further research could usefully be carried out to investigate this.

Before discussing other points raised in this study one last aspect regarding a possible relationship between migraine and epilepsy will be discussed. In section 2.7 it was revealed that one of the female SM group subjects, with no clinical history of epilepsy, showed epileptiform activity unrelated to IPS in her first EEG, but not during a follow-up EEG at a different stage of her menstrual cycle. It was concluded this indicated a low convulsive threshold, possibly related to her menstrual cycle. In a group of 154 people (study subjects, rejected controls and pilot subjects) the finding of one individual (0.6%) with epileptiform activity is not significantly different from the incidence of epilepsy in the population in general (0.5 to 0.6%). However, a second young woman (a pilot subject with NMH) exhibited PCRs during resting with IPS (see above). These two subjects put the incidence of epileptiform activity to 1.2% which is above the population incidence of epilepsy. Similarly, these two student subjects plus the student who acknowledged a history of epilepsy on HQ1, put the known incidence among the 327 students returning HQ1 at 0.9%. This is higher than the incidence of epilepsy in the population, although the difference was not significant. It is difficult to assess the true significance of these findings on the grounds that the figures for the incidence of epilepsy in the population refer to manifest epilepsy and does <sup>not</sup> include individuals, who in the absence of clinical fits show epileptiform activity. No estimates of the incidence of epileptiform activity in the normal population were found. Papers referred to in section 1.10 as suggesting 10 to 15% of the normal population exhibit abnormal EEGs,

did not specify the abnormalities. Without this detailed information the true significance of the observed incidence in this study cannot be assessed.

Besides the interest in any possible links between PSE and VIM, this study also set out to compare VIM patients (CM group) with a set of matched controls having NMH. The procedures used to test these groups were paralleled in two groups of students, one migrainous and one with NMH. It was hoped the use of the migrainous students would indicate whether any particular pattern of responses found in the CM group was specific to VIM or characteristic of the migrainous as a whole. What had not been anticipated was that 84% of the SM group would also indicate visual stimuli could precipitate their attacks of migraine. A possible explanation for this is given in the discussion below.

Before comparing the study groups, the information obtained from medical records on patients attending the Migraine Clinic during the study period, was examined in section 2.4. The disadvantages of using the medical records was mentioned but this was the best source of information available. The precipitants recorded for each patient were analyzed according to groups of precipitant factors and presented in Fig. 2.1 and Table 2.9. The figures were compared with those of previous studies and some discrepancies noted (e.g. low level of psychological factors cited). It was suggested this may be partly lack of recognition by the subject, or else non-reporting. To assess the true relative importance of precipitant factors in the migrainous as a whole would require not only a representative sample drawn from all the migrainous and not just those attending a doctor or specialist

clinic, but also the use of some form of attack diary, as used by Gomersall and Stuart (1973) or by Henryk-Gutt and Rees (1973) as this reduces errors of recall. Such a method has the disadvantage that it requires long-term co-operation of subjects and like other methods does not overcome the reluctance a subject may have to recognize a particular precipitant, e.g. psychological factors or lack of food or oral contraceptives, unless a full diary is kept which allows the investigator to deduce this aspect from the information, e.g. of meal-times and foods consumed in relation to lack of food or known dietary precipitants. It is doubtful whether the information obtained, while of interest, would be of particular use, except insofar as it would aid doctors by indicating the relative importance of precipitants that should be checked for in patients, with the aim of helping the patient avoid them.

Using the information from the medical records patients with VIM were compared with those not affected by visual stimuli to see if they were clearly different on other scores. Overall there was no difference in age of onset, although women with VIM reported their first migraine significantly earlier than non-VIM women patients ( $p < 0.01$ ). It was suggested (page 232) that this may relate to hormonal factors which are known to affect migraine (section 1.6), rather than to any other factor. That the two groups are not fundamentally different was indicated by a comparison of their reported precipitant factors (Fig. 2.2). This revealed that both groups exhibited a similar rank order of precipitants (other than visual stimuli) which suggested any difference was one of degree rather than kind. Those with VIM were more sensitive to other non-visual precipitants than the non-VIM patients with the difference reaching statistical significance for

dietary factors ( $p < 0.01$ ) and other sensory and environmental factors ( $p < 0.05$ ). Based on these findings and given the following assumption, a number of queries were raised. The assumption was that because those triggered by visual stimuli are more easily triggered by all stimuli, they have a lower threshold to migraine attacks. The questions raised were:

- (a) is this because they have a higher level of arousal, whether this be purely arousal of the sympathetic nervous system (see section 1.6) or also involves hyperexcitability of cortical neurons (see section 1.7), and thus they are closer to the threshold for attacks?
- (b) given the abnormalities of biogenic amines and their metabolism (section 1.6 and 1.7) relate to neurological function and have been associated with dietary precipitation of attacks, does the highly significant increase in sensitivity to dietary factors indicate that those affected by visual stimuli show this biochemical abnormality to a greater degree?
- (c) Following from the second question, does the degree of biochemical abnormality (i.e. lack of mono-amine oxidase) relate to severity of migraine and if so, would this contribute to the high level of visual precipitation (84%) found by Bille (1962) in a group of children with pronounced migraine, the lower levels in patient groups and the small proportion indicated by Henryk-Gutt and Rees for a group of civil servants with presumably few severe cases (see section 1.6 and Table 1.4).

This suggestion of a continuum is not new, Hannington-Kiff (1974) and Waters (1975) consider that headaches commonly occurring in the community (migraine and NMH) lie on a continuum. The following quotation is taken from Waters (1975e):

"..... an alternative hypothesis, which has some epidemiological support (Waters and Cochrane, 1970, Waters, 1973b) is that headaches in the community may be represented by a spectrum. At one extreme are mild headaches, usually unaccompanied by other subjective phenomena, and at the other extreme are more severe headaches which are frequently accompanied by the features of migraine. .... When headaches are assessed on a seven-point scale of severity, each of the migrainous features - unilateral distribution of headache, warning that an attack is coming and accompanying nausea - are found to become more frequent in those who report the more severe grades of headaches .... On this hypothesis migraine represents an arbitrary area at one end of a continuous distribution."

To use a somewhat circular argument, if one accepts the argument in the preceeding paragraph that those with VIM are those with severe migraine, one would expect those with severe migraine to have VIM. As the SM group was deliberately composed of those with the most likelihood of having migraine (section 2.2) they were therefore towards the severe end of the headache spectrum, as outlined above, and one would expect a high proportion of VIM. This was indeed the case with 84% affected (section 2.5), a level identical to that found by Bille (1962) in his group of children with pronounced migraine.

Waters (1975e) did not speculate concerning the factors underlying the proposed headache continuum. Some speculation will be made here. If as suggested by the work of people such as Sandler (1977) the migrainous show a trend towards lower and more variable MAO levels and other workers (Belmaker et al, 1974) have suggested other conditions to be related to very high or very low levels of MAO, then the population as a whole could be distributed along a continuum represented by MAO levels. Let us suppose individuals with normal

levels are exposed to a headache precipitant, e.g. mental stress, then their arousal levels would increase and might produce NMH but they would not go over the threshold for attacks, unlike the migrainous individual who, lacking MAO, would already be more highly aroused and thus reach the threshold. This may be over-simplistic in that to produce a migraine attack an individual may be required to have some additional factor to produce the deranged hypothalamic activity and vascular instability although the review of the literature on the pathophysiology of migraine in section 1.7 did not appear to require this. The suggestion of a continuum between migrainous and NMH was supported insofar as the susceptibility to precipitants (both precipitants generally and visual precipitants when examined in detail) showed a continuum from the CM group, through the SM group to the control groups. This was discussed in section 2.5 to which the reader is referred. Such a continuum means that those with migraine and those with NMH cannot be readily distinguished by the precipitants of their headaches, except as regards dietary factors. Dietary factors are of particular interest, for a comparison of the percentages of the subjects affected in the CM and SM groups, while it revealed that, apart from psychological stress, a smaller proportion of the SM group were affected by the different factors, the only factor showing a significant difference was diet ( $p < 0.02$ ). In section 2.4 (and mentioned above) it was shown that VIM patients were significantly more affected ( $p < 0.001$ ) by dietary factors than non-VIM patients and here is a group in which visual stimuli affect a high percentage, but whose members are presumed to suffer less severe migraine than the Clinic patients and who are less affected by diet. While part of this discrepancy may be due to lack of recognition of food as a precipitant by students, it was suggested (section 2.5) that it is still compatible

with the possibility that the degree of biochemical abnormality associated with dietary sensitivity might relate to the severity of migraine.

Further support for a continuum underlying migraine and NMH and an indication that individuals move along that continuum comes from anecdotal reports. For example, it was earlier mentioned (section 1.6) that different stages of the menstrual cycle were associated with changes in the rate of monoamine turnover and women have reported they are differentially sensitive to other precipitants according to the stage of their menstrual cycle, e.g. being unable to watch television when pre-menstrual because it caused a migraine, whereas at other times only NMH would result. Another illustration comes from those people who can eat cheese or chocolate when not fatigued or mentally stressed, but to do so when stressed produces a migraine. This multi-factorial effect could be explained in the following terms and be consistent with the review of the literature in section 1.7 on the pathophysiology of migraine. If the sympathetic nervous system (adrenergic system) is unusually active, or, conversely, if the serotonergic system is at an unusually low level of activity, then any event acting to further increase adrenergic system functioning, or to further decrease serotonergic system functioning (including depletion of serotonin from the brain), results in critical imbalance of functioning which manifests as a migraine attack.

As yet the electro-physiological findings have not been discussed. The expectation that the migrainous would demonstrate an extended flicker response and that the control subjects would not do so was unfulfilled. Explanations for these unsatisfactory findings were sought.



Four alternatives were considered:

- (a) That manual frequency analysis is inadequate. Certainly as the rate of IPS was increased it became more difficult to distinguish photic driving from muscle artefact. However it was the migrainous who demonstrated most muscle artefact, and therefore when the extended flicker response was present it could more easily be distinguished in the EEGs of controls.
- (b) The H response as distinguished using the BNI type wave analysers was a product of the equipment rather than the subjects. The comment of Fukushima (1975) that the Walter type wave-analyser using band pass filters and integrators is not reliable because of artefacts contamination has already been made. It is well known that such analysers tend to 'beat' and produce false harmonics and this may partly account for the high incidence of harmonics found by Townsend (1967). Despite these drawbacks the frequency analysis did distinguish between the migrainous H response and the normal N response. Moreover, Bille (1962) using visual inspection and a rating procedure found some degree of photic driving by fast frequencies in 92% of the migraine children as compared to 77% of the controls, a difference that was probably significant ( $p < 0.05$ ). Why the control children should show such a high incidence of extended driving was not explained. Equally, it remains unexplained why Friedman and Pampiglioni (1974) using visual inspection found an extended driving response in only 46% of the 160 migrainous children they studied and

Domzal (1975) found only 25% of his group showed an II response. Thus an extended flicker response is not a matter of machine artefact but does not appear to be specific for migraine.

- (c) The mode of presentation of the IPS may affect results. Golla and Winter (1959), Smyth and Winter (1964), Townsend (1967) and Slatter (1968) when presenting their IPS, changed the rate progressively during continuous stimulation, and they all found the extended flicker response in the migrainous. Bille (1962) used both a progressively changing stimulus and discrete bursts of IPS at different flash rates, but does not say which he rated to produce the figures (quoted above) indicating an extended response. This study used discrete presentation of IPS, following the recommendations of Jeavons (1969) and with the intention of identifying which IPS rates, if any, evoked abnormalities in the EEG. Further research would be needed to establish whether this variation in the mode of presentation significantly affects the findings.
- (d) An extended flicker response is associated with some factor other than migraine, but that that factor tends to be associated with migraine.

The literature was then examined for a possible factor and as will be argued below, that factor could be physiological arousal. The argument rests on the following information:

- (a) The work of Montagu (1967) suggests the quantity of photic driving at any particular IPS rate is related to the degree of activity (c/sec.) seen at that rate in the basic EEG. Montagu suggested the presence of beta activity produced the increased responses to the tested rates of 20 and 24 f/sec. Thus normal relaxed individuals with prominent activity in the alpha range would be expected to show a photic driving response at that range (the N response); those with limited beta might show an A response and those with extensive fast activity in the basic EEG an H response. This relationship between background activity would need to be verified by further research as this relationship was not confirmed by Fukushima (1975).
- (b) Assuming the relationship postulated between background activity and the photic driving response holds good, then one would predict that conditions associated with an increase in beta activity would show an extended flicker response. In section 1.8 it was mentioned that increased anxiety is associated with a generalized increase in beta activity and anxiety states have been associated with an extended flicker response (Ulett, Glesor, Winokur and Lawler, 1953; Shagass, 1955).
- (c) As discussed in section 1.6 the only psychological trait consistently found in the migrainous as a group is that they tend to show higher levels of anxiety than normals. Thus one would expect them to show a trend towards increased levels of beta activity, such a trend was reported by Ulett et al (1952), Boudin et al (1962) and Friedman and Pampiglione (1974). Thus if the

relationship between beta and an extended flicker response holds good one would expect them to show an extended flicker response such as Golla and Winter (1959) and others have found.

From this discussion a further suggestion will be made to explain the findings of earlier authors and then an attempt to explain the findings of this study. As was noted above the incidence of the H response observed in the migrainous varies from 25% (Domzal, 1975) to over 90% (Bille, 1962; Smyth and Winter, 1964). It is possible that the degree of anxiety experienced by the patients in the different recording situations might account for the varying results. Degree of anxiety experienced by the subjects of this study might also have produced the unexpected photic driving findings. While treatment of subjects during the electrophysiological recordings was kept as identical as possible, their pre-treatment was not identical. The CM group were all interviewed by the experimenter prior to their visit to the Neuropsychology Unit. Thus rapport had been established with the VIN patients, who had also had a relatively full explanation of what the test would involve, and in many cases had also discussed (in the Migraine Clinic waiting-room) the test with other patients who had already completed the test. Thus their level of anxiety could be expected to be less enhanced relatively than that of the majority of their matched control subjects who had not had the benefit of previously meeting the experimenter, or of reassurance regarding the test by the experimenter or other people (unless a friend had co-operated). If one accepts that the controls would generally show normal levels of anxiety but the situation was more anxiety provoking for them because of pre-treatment differences,

in contrast to the CM group who are expected to show higher than normal levels of anxiety generally but who found the situation less anxiety provoking, one could end up with both groups at similar points on the arousal scale, with a similar incidence of background beta activity and so similar photic driving responses. If Table 2.22 is examined for the diffuser condition (the stimulus used by previous authors) the photic driving results for the CM and CC groups show no difference in the incidence of the N response, although the CC group shows more A and less H responses, perhaps indicative of a trend to less anxiety and less beta activity. The incidence of beta in the two groups is difficult to assess accurately because of muscle artefact (especially in the migrainous) but generalized or posterior beta was identified in 28 of the 45 people in the CC group (62.2%) which is approaching the combined incidence of A and H responses (76%).

On the basis of this argument the students, who received the same pre-treatment and should therefore be matched for experimentally induced anxiety, should show a trend for the SM group (supposedly more anxious, or aroused as a consequence of migraine) to exhibit a greater percentage of A and H types and this is indeed the case with 72% of the SM group as opposed to 63% of the SC group showing an A or H type response. Why the small number of SF students should show such a high incidence of the H response is a matter for speculation.

A further re-examination of the literature was undertaken to check on the source of normal subjects in previous studies. The paper by Golla and Winter (1959) used 50 control subjects composed of 15 epileptic patients (who may have had previous EEGs and therefore be used to the

test situation) and 35 normal people (but one is not informed whether they are members of staff of the Institute, who could be expected not to be anxious, or outsiders). Lehtonen (1974) stated his control subjects were eleven female nurses, and therefore they would not be expected to be anxious. It is therefore not surprising they showed a significantly lower VEP response at 22 f/sec. than the controls, (this was the only IPS rate he used in the beta range). On the grounds of equivalent naivety of migrainous and control subjects the study by Giel et al (1966) is a good example. His control group consisted of 100 male workers, who had no complaints, took no medicine, were normally occupied and were referred for an EEG before they had to take part in the production of insecticides. Unfortunately they did not investigate photic driving responses.

There are a number of difficulties regarding the explanation for observed photic driving responses. The work of Vogel and his co-workers on photic driving and MAO levels has already been criticized (see section 1.10). In another paper (Vogel, Broverman, Klaiber and Kun, 1969) they investigated photic driving as a function of cognitive style. They suggested that driving responses are decreased by substances which produce an adrenergic state, which is contrary to the argument above. However, as with the reports mentioned above, it is difficult to assess the influence of IPS rate and the influence of stimulus intensity from their report. They quote Ulett and Gleser (1952) as supporting the statement that:

"As might be expected increased driving is associated with trophotropic behaviours and decreased driving is associated with ergotropic behaviours".

On investigation it was found that Ulett and Gleser (1952) used only one rate of IPS, that is 14 f/sec. and while those undergoing experimental stress showed a reduction in photic driving at this rate, one cannot know what changes would have occurred at other frequencies and one does not know what changes if any, occurred in the resting EEG, i.e. was there a shift away from 14 f/sec.?

This discussion has talked about 'arousal' and it is not unusual for authors to use this as a general term (e.g. Mills, 1975), but a recent paper makes it clear (Asso, 1978) that one should differentiate behavioural, autonomic and cortical arousal. Asso considers a number of studies purporting to measure cortical arousal and concludes there are considerable difficulties in finding valid indices of cortical arousal. It is suggested some fundamental research in this area is needed.

The points made and conclusions drawn in the above discussion on precipitated factors and photic driving in the migrainous and the controls are summarized below:

- (a) No new suggestions for the mechanisms which enable visual stimuli to precipitate migraine are proposed (see section 1.6).
- (b) The above susceptibility of the different groups studied to certain precipitants of headache (migraine or NMH) supported an earlier suggestion of a continuum underlying migraine and other common headaches (see sections 2.4 and 2.5).
- (c) The only group of precipitant factors to clearly differentiate the migrainous and controls was that of dietary factors. Within the migrainous there were significant differences in the susceptibility to dietary factors. The query was

raised as to whether the degree of susceptibility to dietary factors reflected the reduced MAO functioning thought to be associated with migraine. Further research would be needed to answer this.

- (d) The photic driving results were unexpected and were discussed in terms of differing levels of arousal, and a chain of events from reduced levels of MAO, through imbalance of the adrenergic and serotonergic systems (autonomic arousal), cortical arousal and background EEG changes associated with anxiety or arousal, to an assumed relationship between background and the range of IPS to which photic driving is observed.

Not only does such a chain of events need to be proved, but so do the assumptions (explicit and implicit) contained within it need to be verified, for while there is some support for them in previous work, there are also contradictory or unclear findings. The suggestions for further research that arose in the literature review as well as in this section or section 2 are summarized below.



A summary of suggestions for further research arising from the review of the literature and the experimental findings of this study

1. Scientific research on migraine (as opposed to clinical observations) should employ diagnostic criteria, which should be clearly stated and rigorously applied, not only for the selection of migrainous individuals for the experimental group, but also for the exclusion of those likely to be migrainous from the control groups (see sections 1.2, 1.3, 1.9, 1.10, 2.2 and 3.0).
  
2. To avoid difficulties in interpretation of results people with conditions likely to complicate analysis of EEG and VEP results should be excluded from both experimental and control groups, including those with a history of severe head injury (section 2.2); with inadequate visual acuity, if pattern stimulation is used (sections 1.8 and 2.6) or, in studies such as this, people with retinal thrombosis or other permanent reduction of their visual fields, who, while of interest in themselves (sections 1.4 and 1.10), would complicate the final analysis of results.
  
3. The author supports the suggestions of Parsonage (1975) that further research on the EEG and migraine (section 1.10) should
  - (a) Determine the incidence of EEG abnormalities in migraine in more representative samples of the migraine population.
  - (b) Clarify the significance of the instability of EEG appearances during hyperventilation.
  - (c) Seriously question the existence of a link between migraine and epilepsy (see below).

- (d) Investigate the usefulness of anticonvulsants in migraine (see below).
  - (e) Investigate the significance of the extended range of response to flicker (see below).
4. Concerning a possible relationship between migraine and epilepsy (section 1.9) the following is suggested:
- (a) EEG studies of representative samples of the whole migrainous population be done to establish to what extent paroxysmal activity in the migrainous is a chance association, reflects a common cause or is caused by migraine (section 1.9 and 1.10).
  - (b) The work of Scott, Moffett and Swash (1972) indicating tyramine (a dietary precipitant of migraine) accentuates paroxysmal EEG features (i.e. alters convulsive thresholds) should be followed up (sections 1.9 and 3.0).
  - (c) To aid differential diagnosis of migraine and epilepsy adequate comparisons between the headaches and the abdominal sensations that occur in the two conditions should be made (section 1.9).
  - (d) There is a paucity of literature comparing the neuronal biochemistry of migraine and epilepsy, and such a comparison might resolve the question of any common origin for migraine and epilepsy.
  - (e) Section 1.9.6 briefly considered anticonvulsants as therapy in migraine and the following conclusion and suggestion were made.

"Perhaps the anticonvulsants such as phenytoin act to fill the short-fall of inhibitory action, due to the dysfunction of the serotonergic system, and so reduce the over-arousal of the hypothalamus and other structures served by the serotonergic system, such that they stay within normal limits. Further research upon phenytoin and other anti-convulsants with a similar mode of action, known to be effective in the treatment of disorders of central pain-perception would help answer the controversy on whether epilepsy and migraine share a common bio-chemical or electro-chemical basis."

5. This research indicated that while VIM and PSE may be precipitated by similar visual stimuli and show similar sex ratios, they are two distinct conditions, as indicated by differences in distribution of age of onset; proportions affected by different visual stimuli and their EEG and VEP characteristics. However, it is suggested further research is required to establish what neuronal and biochemical features differentiate these two conditions from each other and from normals. (section 1.9, 2.4, 2.5, 2.7 and 3.0).
6. The possible relationship between migraine and hypertension needs clarifying both with regard to the extent and the nature of such a relationship (sections 1.5 and 1.6).
7. Although an extensive list of factors regarded as migraine precipitants is available, the relative importance of these within the migraine population generally remains to be clarified, both in terms of the percentages of people ever affected by such precipitants and in terms of the relative importance of those precipitants to individuals. Such information would aid treatment by indicating those factors which should be most urgently investigated with regard to elimination or modification and thus prevention of attacks (sections 1.6, 2.4, 2.5 and 3.0).

8. This thesis has not considered therapies or preventative measures in detail. With regard to visual precipitants it is suggested research into the following may prove beneficial

- (a) the use of glasses incorporating lenses of the type devised by Harding, Drasdo, Kabrisky and Jeavons (1969) for use with photosensitive epileptics and described by Jeavons and Harding (1975). These may prove useful for prevention of VIM (section 1.6 and 3.0).
- (b) complaints regarding fluorescent lighting suggest migraine may be prevented, and the comfort of the non-migrainous improved if measures are taken to reduce noticeable oscillations of light from the tubes (section 2.5). No literature review was undertaken to see if research has established whether the use of diffuser screens and/or the installations of paired tubes using the push-pull system would be sufficient and relatively inexpensive measures to produce such improvement.
- (c) Whether modification of lighting in vehicular tunnels be carried out so as to provide appropriate lighting levels without a flicker effect from
  - (i) side-lights
  - (ii) overhead lighting(sections 1.6 and 2.5).

9. No work appears to have been done on fumes and odours, as precipitants of migraine, with regard to their biochemical constituents and the allergic, vasoactive or biochemical reactions these produce in the body (section 1.6).

10. Continued research into pathogenesis of migraine generally (section 1.7) particularly regarding:
  - (a) serotonin releasing factors
  - (b) associated changes in autonomic and central arousal
  - (c) influence of other factors (including precipitants, section 1.6)
  - (d) association between central pain perception and serotonin hypothesis of migraine
  - (e) establish to what extent platelet MAO activity (accessible to experimenters) reflects central MAO activity (which is inaccessible in intact humans).
11. In section 3 a tentative hypothesis was outlined suggesting a chain of events from a headache continuum (NMH to migraine); underlying which was suggested a continuum of decreasing MAO levels associated with increasing levels of arousal; changes in background EEG activity and, consequently, to altered photic driving responses. Clearly further research is needed to establish such a chain of events exists. Evidence was presented to support the assumptions made but much of this needs verification, as there is not universal agreement. Individual aspects of research pertinent to this are listed below.
12. The work of Sandler and others (section 1.6 and 1.7) suggests the migrainous show lower and more variable MAO levels. This study asks whether the migrainous and those with NMH should be regarded not as having distinctly different levels of MAO but as lying on a continuum of MAO levels (or MAO activity) and that individuals may move up or down that continuum according to influences from the external, or within the internal,

environment. Further research is needed to establish or disprove this.

13. The findings in sections 2.4 and 2.5 indicate that a continuum (as suggested in No. 11 above) may exist between the migrainous and those with NMH. Because of the direction of the findings and the significant differences in sensitivity to dietary factors it was queried not only if the degree of biochemical abnormality (lack of MAO) related to severity of migraine (see No. 12 above), but also whether this related to susceptibility to visual precipitants. Such a relationship would need to be verified by further research.

14. The influence of the menstrual cycle on migraine is receiving attention from a number of authors (sections 1.6 and 1.7) and Greene (1975) concluded future researchers will concentrate

"upon the effects of hormones on autonomic activity and on the actions of substances that influence this such as serotonin, the catecholamines and the enzymes that oppose them, ..... and other substances."

This is important as it is possible the low MAO levels and associated arousal changes seen in migraine (section 1.7) may also influence PD. It is suggested the work of Vogel and others (sections 1.8 and 3.0) regarding the hormonal changes in the menstrual cycle, the associated changes in MAO activity and alterations in PD should be repeated with the following modifications:

- (a) automated analysis of the background activity and of the PD should be carried out and examined for a possible relationship

- (b) the results should be presented so that the effects of changes in flicker rate and changes in intensity can be distinguished.
15. Independent of work on the menstrual cycle, the findings of Montagu (1967) should be tested to verify whether the presence of beta activity in the resting EEG is associated with the appearance of photic driving at 20 f/sec. and over, and thus an apparent extension of the H response.
  16. Given research supports the contention in the suggestion for further research number 15, do the migrainous show a tendency for excessive generalized or posterior beta activity and is it these individuals who show the extension of photic driving? (sections 1.10, 2.7 and 3.0).
  17. The tentative hypothesis referred to in number 11 above assumes a higher level of arousal, whether of the autonomic nervous system or of the cortex, will be associated with changes in background EEG (increased beta) and an extended photic driving response. However, as the report of Asso (1978) indicates, there is a need for fundamental research work to establish what are viable indices of cortical arousal.
  18. In view of the discussion on how levels of arousal may affect the range of photic driving and in the knowledge that the migrainous tend to exhibit greater anxiety and higher autonomic arousal, a revised methodology for the selection of subjects is needed. It is suggested that in addition to the usual controls of age and sex matching, exclusion of complicating factors (see above), etc. (see section 1.8), subjects should:

- (a) be equated for naivety (or experience) of the tests to be used,
- (b) be given identical pretreatment.

It was discussed in section 3 how the non-matching of the CM and CC groups for pre-treatment may have contributed to the lack of difference in the photic driving results, and therefore the need for this revised selection methodology.

19. In addition to the revised selection methods above, intended to equate for experimental stress it would aid interpretation of results if additional measures were taken, for example
  - (a) an index of anxiety such as the IPAT anxiety scale mentioned by Hay (1973),
  - (b) an index of autonomic balance such as that mentioned by Wenger (1966),
  - (c) electrophysiological indices of autonomic activity, e.g. heart rate and galvanic skin response.
20. If anxiety does affect the photic driving responses and the migrainous and those with NMH move along a continuum, then if carefully selected and matched subjects (see above) are recorded on two occasions (with stage of the menstrual cycle controlled) then one may demonstrate such a continuum and variation by virtue of the first recording being assumed to induce more anxiety in a naive subject than the second recording.
21. In sections 1.8 and 1.10 it was noted Richey et al (1966) had found significant differences in pupillary diameter in a direction opposite to that expected with sympathetic dominance but consistent with a physiological defence against excess light.



Verification of this finding and establishing the underlying cause is a subject for further research.

22. The findings of previous studies of the VEP and different levels of platelet MAO were at variance (section 1.8). It was suggested further studies are needed.
23. If migraine is related to MAO levels (or MAO activity), then the work suggested above (number 22) is essential in interpreting VEP findings in migraine. It is suggested future VEP studies in migraine should:
  - (a) follow the recommendations above concerning selection of subjects and monitoring of arousal levels,
  - (b) measure the MAO levels (or MAO activity) of subjects at the time of recording.

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(See also Addenda to Bibliography)

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## APPENDIX 1

### CLASSIFICATION OF HEADACHE

This classification is reproduced from Vinken and Bruyn (1969). The classification was prepared by the Ad Hoc Committee on Classification of Headache of the National Institute of Neurological Diseases and Blindness (1962). The members of the committee being Arnold P. Friedman (Chairman), Knox H. Finley, John R. Graham, E. Charles Hunkle, Adrian M. Ostfeld and Harold G. Wolff.

#### 1. VASCULAR HEADACHE OF MIGRAINE TYPE

Recurrent attacks of headache, widely varied in intensity, frequency, and duration. The attacks are commonly unilateral in onset; are usually associated with anorexia and, sometimes, with nausea and vomiting; in some are preceded by, or associated with, conspicuous sensory motor and mood disturbances; and are often familial. Evidence supports the view that cranial arterial distention and dilatation are importantly implicated in the painful phase but cause no permanent changes in the involved vessel. Listed below are particular varieties of headache, each sharing some, but not necessarily all, of the above-mentioned features:

- A. 'Classic' migraine - Vascular headache with sharply defined, transient visual, and other sensory or motor prodromes or both.
- B. 'Common' migraine - Vascular headache without striking prodromes and less often unilateral than A and C. Synonyms are: 'atypical migraine' or 'sick' headache. Calling attention to certain relationships of this type of headache to environmental, occupational, menstrual, or other variables are such terms as 'summer', 'Monday', 'weekend', 'relaxation', 'premenstrual', and 'menstrual' headache.

C. 'Cluster' headache - Vascular headache, predominantly unilateral on the same side, usually associated with flushing, sweating, rhinorrhea, and increased lacrimation: brief in duration and usually occurring in closely packed groups separated by long remissions. Identical or closely allied are: erythroprosopalgia (Bing); ciliary or migrainous neuralgia (Harris); erythromelalgia of the head or histaminic cephalgia (Horton); and petrosal neuralgia (Gardner et al).

D. 'Hemiplegic' migraine and 'ophthalmoplegic' migraine - Vascular headache featured by sensory and motor phenomena which persist during and after the headache.

E. 'Lower-half' headache - Headache of possibly vascular mechanism, centered primarily in the lower face. In this group there may be some instances of 'atypical facial' neuralgia, sphenopalatine ganglion neuralgia (Sluder), and vidian neuralgia (Vail).

## 2. MUSCLE-CONTRACTION HEADACHE

Ache or sensations of tightness, pressure, or constriction, widely varied in intensity, frequency, and duration, sometimes long-lasting, and commonly suboccipital. It is associated with sustained contraction of skeletal muscles in the absence of permanent structural change, usually as part of the individual's reaction during life stress. The ambiguous and unsatisfactory terms 'tension', 'psychogenic', and 'nervous' headache refer largely to this group.

## 3. COMBINED HEADACHE: VASCULAR AND MUSCLE-CONTRACTION

Combinations of vascular headache of the migraine type and muscle-contraction headache prominently coexisting in an attack.

#### 4. HEADACHE OF NASAL VASOMOTOR REACTION

Headaches and nasal discomfort (nasal obstruction, rhinorrhea, tightness, or burning), recurrent and resulting from congestion and edema of nasal and paranasal mucous membranes, and not proven to be due to allergens, infectious agents, or local gross anatomic defects. The headache is predominantly anterior in location, and mild or moderate in intensity. The illness is usually part of the individual's reaction during stress. This is often called 'vasomotor rhinitis'.

#### 5. HEADACHE OF DELUSIONAL, CONVERSION, OR HYPOCHONDRIACAL STATES

Headaches of illnesses in which the prevailing clinical disorder is a delusional or a conversion reaction and a peripheral pain mechanism is non-existent. Closely allied are the hypochondriacal reactions in which the peripheral disturbances relevant to headache are minimal. These also have been called 'psychogenic' headaches.

#### 6. NON-MIGRAINOUS VASCULAR HEADACHES

Headaches associated with generally non-recurrent dilatation of cranial arteries:

A. Systemic infections - usually with fever.

B. Miscellaneous disorders - including hypoxic states, carbon monoxide poisoning, effects of nitrites, nitrates, and other chemical agents with vasodilator properties, caffeine-withdrawal reactions, circulatory insufficiency in the brain (in certain circumstances), postconcussion reactions, postconvulsive states, 'hang-over' reactions, foreign-protein reactions, hypoglycemia, hypercapnia, acute pressor reactions (abrupt elevation of blood pressure, as with paraplegia or

pheochromocytoma), and certain instances of essential arterial hypertension (e.g. those with early morning headache).

## 7. TRACTION HEADACHE

Headaches resulting from traction on intracranial structures, mainly vascular, by masses:

- A. Primary or metastatic tumors of meninges, vessels, or brain.
- B. Hematomas (epidural, subdural, or parenchymal).
- C. Abscesses (epidural, subdural, or parenchymal).
- D. Post-lumbar-puncture headache ('leakage' headache).
- E. Pseudotumor cerebri and various causes of brain swelling.

## 8. HEADACHE DUE TO OVERT CRANIAL INFLAMMATION

Headaches due to readily recognized inflammation of cranial structures, resulting from usually non-recurrent inflammation, sterile or infectious.

A. Intracranial disorders - infectious, chemical, or allergic meningitis, subarachnoid hemorrhage, post-pneumoencephalographic reaction, arteritis, and phlebitis.

B. Extracranial disorders - arteritis and cellulitis.

## 9. HEADACHE DUE TO DISEASE OF OCULAR STRUCTURES

Headache due to spread of effects of noxious stimulation of ocular structures (as by increased intraocular pressure, excessive contraction of ocular muscles, trauma, new growth, or inflammation).

#### 10. HEADACHE DUE TO DISEASE OF AURAL STRUCTURES

Headache due to spread of effects of noxious stimulation of aural structure (as by trauma, new growth, or inflammation).

#### 11. HEADACHE DUE TO DISEASE OF NASAL AND SINUSAL STRUCTURES

Headache due to spread of effects of noxious stimulation of nasal and sinus structures (as by trauma, new growth, inflammation, or allergens).

#### 12. HEADACHE DUE TO DISEASE OF DENTAL STRUCTURES

Headache due to spread of effects of noxious stimulation of dental structures (as by trauma, new growth, or inflammation).

#### 15. HEADACHE DUE TO DISEASE OF OTHER CRANIAL AND NECK STRUCTURES

Headache due to spread of pain from noxious stimulation of other structures of the cranium and neck (periosteum, joint, ligaments, muscles, or cervical roots).

#### 14. CRANIAL NEURITIDES

Caused by trauma, new growth, or inflammation.

#### 15. CRANIAL NEURALGIAS

Trigeminal (tic douloureux) and glossopharyngeal. The pains are lancinating ('jabbing'), usually in rapid succession for several minutes or longer; are limited to a portion or all of the domain of the affected nerve; and are often triggered by end-organ stimulation. Trigeminal neuralgia must be distinguished, in particular, from cluster headache (IC), with which it is often confused.

N.B.

1. The types mentioned under 1 to 5 represent the major clinical disorders dominated by headache - those which are particularly common, and in which headache is frequently recurrent and disabling.

2. So-called chronic post-traumatic headache may arise from any one of several mechanisms. Such headache may represent sustained muscle contraction (2); recurrent vascular dilation (1B); or rarely, local scalp or nuchal injury (15); in some patients the post-traumatic pain is part of a clinical disorder characterized by delusional, conversion or hypochondriacal reactions (5).

(Note: The numbers in brackets after each item above refer to the sections in the text of this Appendix).

This questionnaire was developed by Dr.W.E.Waters and is reproduced with the author's permission.

CONFIDENTIAL

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## Headache Questionnaire

Number

--	--	--	--	--

Surname..... Mr./Mrs./Miss

Christian Names.....

--

Address .....

Date of Birth.....

--	--

What is (or was) your main occupation? Job.....

Industry.....

If you are a married woman, what is (or was) your husband's main occupation?

--	--

Job.....

Industry.....

1. Have you had a headache within the past year?

YES  
NO

Please  
tick  
one

--

If NO:—Have you ever had a headache in your life?

YES  
NO

IF YOU HAVE HAD A HEADACHE DURING THE PAST YEAR, PLEASE ANSWER ALL THE QUESTIONS  
BELOW FOR YOUR HEADACHES DURING THE PAST YEAR ONLY. WE DO NOT WANT DETAILS  
OF ANY HEADACHES THAT HAPPENED MORE THAN ONE YEAR AGO, UNLESS SPECIALLY  
MENTIONED.

IF YOU HAVE NOT HAD A HEADACHE DURING THE PAST YEAR, PLEASE TURN TO THE LAST PAGE.

2. Are your headaches usually mild or severe; or do you get both mild and severe headaches?

Mild  
Severe  
Both

Please  
tick  
one

--

If you get both mild and severe headaches:—

Are they different kinds of headache, that is can you clearly distinguish between them?

YES  
NO

IF YOU GET MILD OR SEVERE HEADACHES, PLEASE CONTINUE WITH THE FOLLOWING QUESTIONS.

IF YOU GET BOTH SEVERE AND MILD HEADACHES, PLEASE ANSWER ALL THE QUESTIONS FOR YOUR SEVERE HEADACHES ONLY.

3. Which one of these statements is nearest the truth for you?

--

My headaches are very mild.  
My headaches are mild.  
My headaches are not usually severe.  
My headaches are quite severe.  
My headaches are very severe.  
My headaches are terribly severe.  
My headaches are almost unbearable.

Please  
tick  
one

4. Which of these statements is nearest the truth for you?

- I hardly notice my headaches at all.  
My headaches rarely inconvenience me.  
My headaches sometimes distract me from what I am doing.  
Sometimes I am unable to continue my normal activities because of my headaches.  
My headaches sometimes interfere a lot with what I am doing.  
I can hardly do anything when I have a headache.  
I am absolutely fit for nothing when I have a headache.

Please  
tick  
one

☐

5. How long do your headaches usually last? .....

☐

6. (a) When you have a headache, do you usually have to:—

- lie down?  
rest?  
take things easy?

Please  
tick  
if applicable

☐

If you do—For how long is this usually? .....hrs.

(b) Have you missed work during the past year because of a headache?

YES  
NO

Please  
tick  
one

☐

If YES, for how many days? .....

7. Do you get a headache:—

- about once a year?  
several times a year?  
about once a month?  
several times a month?  
about once a week?  
several times a week?  
(include all headaches, mild and severe).

Please  
tick  
one

☐

8. Are your headaches throbbing or thumping?

- never?  
sometimes?  
usually?  
always?

Please  
tick  
one

☐

9. Where do you usually feel the headaches?

- temples  
forehead  
back of head  
top of head  
all one side  
all over the head  
if elsewhere, where.....

Please  
tick  
one

☐

10. Are your headaches on <sup>one</sup> side only:—

- never?  
sometimes?  
usually?  
always?

Please  
tick  
one

☐

11. Before you get a headache do you know that one is coming?

YES  
NO

Please  
tick  
one

☐

If you do, please describe briefly what you notice .....

---

---



12. When you have a headache do you notice any changes in your sight?

YES  
NO

Please  
tick  
one

☐

If YES, please describe briefly what you notice .....

.....  
.....

13. When you have a headache do you:—

lose your appetite?  
feel dizzy?  
feel sleepy?  
hear ringing in your ears?  
find that light hurts your eyes?  
notice tingling, or any strange feeling in any part of your body?

Please  
tick  
any  
that  
apply

☐

14. When you have a headache do you:—

ever feel sick?  
usually feel sick?  
ever vomit?  
usually vomit?  
always vomit?

Please  
tick  
any  
that  
apply

☐☐

15. Have you ever seen a doctor about the headaches?

YES  
NO

Please  
tick  
one

☐

If YES, have you seen a doctor about the headaches during the past year?

YES  
NO

16. Over the years have your headaches become:—

more frequent?  
less frequent?  
or have you noticed no change?

Please  
tick  
one

☐

17. Over the years have your headaches become:—

more painful?  
less painful?  
or have you noticed no change?

Please  
tick  
one

☐

AND NOW SOME QUESTIONS ABOUT YOUR GENERAL HEALTH

Please Tick the Correct Answer like this—					YES ✓ or	NO ✓
18.	Do you suffer from indigestion?	—	—	—	YES	NO
19.	Were you ever subject to bilious attacks?	—	—	—	YES	NO
20.	Are you worried about your weight?	—	—	—	YES	NO
21.	Were you ever subject to travel sickness?	—	—	—	YES	NO
22.	Were you ever subject to frequent attacks of pain in your stomach?	—	—	—	YES	NO
23.	Does every little thing get on your nerves and wear you out?	—	—	—	YES	NO
24.	Are you considered a nervous person?	—	—	—	YES	NO
25.	Have you ever had skin trouble (eczema)?	—	—	—	YES	NO
26.	Do skin cuts take a long time to heal?	—	—	—	YES	NO
27.	Have you ever worn glasses?	—	—	—	YES	NO
28.	Are you extremely shy or sensitive?	—	—	—	YES	NO
29.	Are you considered a touchy person?	—	—	—	YES	NO
30.	Do you suffer from frequent colds?	—	—	—	YES	NO
31.	Have you ever had sinus trouble?	—	—	—	YES	NO
32.	Are you constantly keyed up and jittery?	—	—	—	YES	NO
33.	Do you suffer from severe nervous exhaustion?	—	—	—	YES	NO
34.	Have you ever had a severe head injury?	—	—	—	YES	NO
	If YES, were you unconscious?	—	—	—	YES	NO
35.	Have you ever had an epileptic fit?	—	—	—	YES	NO
36.	Do you wear yourself out worrying about your health?	—	—	—	YES	NO
37.	Do you suffer from rheumatism?	—	—	—	YES	NO
39.	Do you smoke?	—	—	—	YES	NO
	If YES, roughly how many cigarettes a day?	—	—	—		
	or how many ozs. of tobacco a week?	—	—	—		


WE ARE MOST GRATEFUL TO YOU FOR HELPING IN THIS WORK

CONFIDENTIAL

Number.....

HEADACHE QUESTIONNAIRE 2

Surname ----- Mr/Mrs/Miss

Christian or Fore-names -----

Address -----

SECTION 1

WHETHER OR NOT YOU SUFFER FROM HEADACHES PLEASE ANSWER ALL QUESTIONS  
IN THIS SECTION

1. Are you

Right-handed

Left -handed

Ambidextrous (use both hands equally for everything)

Ambilatera: (use one hand for some things and the other hand for  
for other things)

please  
tick  
correct  
answer

2. During childhood did you suffer from any of the following?

Frequent attacks of vomiting (including bilious attacks) YES NO

Travel sickness YES NO

Frequent attacks of pain in your stomach YES NO

Skin trouble (eczema) YES NO

Frequent attacks of indigestion YES NO

Hay fever YES NO

Asthma YES NO

Epileptic fits YES NO

Head Injury (i.e. fracture, concussion or knocked  
unconscious) YES NO

please  
tick  
correct  
answer

If you had a head injury please give details including:

How did the injury occur -----

Where on the head was the injury -----

How old were you -----

3. Some questions about the general health of you and your family.

Below are listed a number of illnesses and disorders. By the side  
of these, please list which of your close BLOOD RELATIVES (i.e.  
grandparents, parents, brothers and sisters, children or grand-  
children) are known to suffer or have suffered from them. If you  
suffer or have suffered from any of these please put SELF.

1. Migraine (throbbing headache) -----

2. Cluster headache, (i.e. severe, one-sided, head or facial pain,  
lasts for minutes or hours, often associated with "crying" of  
the eye on the painful side. Usually recurs once or more daily  
for periods of weeks or months followed by weeks or months without  
pain) -----

3. Tension headache (muscle contraction headache - ordinary headache - aching pain) \_\_\_\_\_
4. Trigeminal neuralgia (i.e. Intermittent or paroxysmal sharp pains of eye and face on one side of the head) \_\_\_\_\_
5. Recurring periods of temporary blindness \_\_\_\_\_
6. Recurring periods of blurred vision \_\_\_\_\_
7. Recurring periods of "seeing flashing lights" or other visual disturbances \_\_\_\_\_
8. Stomach Ulcer \_\_\_\_\_
9. Hypertension (on testing by a doctor found to have high blood pressure) \_\_\_\_\_
10. Coronary thrombosis \_\_\_\_\_
11. Hay fever \_\_\_\_\_
12. Other allergies \_\_\_\_\_
13. Asthma \_\_\_\_\_
14. Skin trouble (eczema ) \_\_\_\_\_
15. Frequent vomiting attacks (including bilious attacks ) \_\_\_\_\_
16. Frequent attacks of stomach pains \_\_\_\_\_
17. Frequent indigestion \_\_\_\_\_
18. Travel sickness \_\_\_\_\_
19. Vertigo (feeling that the world is revolving round you or that you are revolving in space) \_\_\_\_\_
20. Epilepsy \_\_\_\_\_
21. Sinus trouble \_\_\_\_\_
22. Spontaneous bruising (bruises occur without the area being hit) \_\_\_\_\_

- 
4. Below are a list of a number of disorders which MAY or MAY NOT be associated with headaches, and may be permanent (lasting) or temporary (short-lived). We wish to know if you have EVER suffered any of these. Do NOT include occasions when there has been an obvious cause e.g. bloodshot eyes due to a hangover or watering nose due to a cold or hay-fever.

Please tick correct answer

EXAMPLE: Diplopia (seeing double)

YES NO

If the answer is YES and the disorder is or was associated with a headache, please put 'H' by the side of the answer

EXAMPLE: Diplopia (seeing double)

YES<sup>H</sup> NO

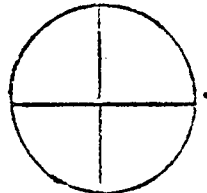
1. Photophobia (cannot bear strong light)

YES NO

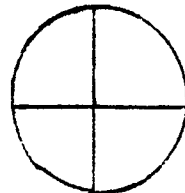
2. Blurred vision

YES NO

If YES, in the diagrams below please shade areas of vision which become blurred



Left eye area  
of vision

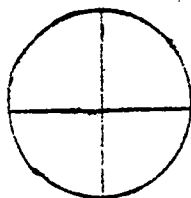


Right eye area  
of vision

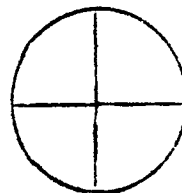
3. Scotomas (temporary blindness or partial blindness)

YES NO

If YES, in the diagram below please shade in the areas of vision which are lost (i.e. blind patches).



Left eye area  
of vision



Right eye area  
of vision

4. Other visual disturbances e.g. seeing flashing lights, dazzling display of coloured lights, spots or lines distortions of size or of space, etc.

YES NO

If YES, please give details

-----  
-----

YES NO

5. Bloodshot eye or eyes

If YES, which is usually affected?

Please tick one of the below

right eye

left eye

both eyes

YES NO

6. Watering eye or eyes

If YES, which is usually affected?

Please tick one of the below

right eye

left eye

both eyes

- |     |  |     |    |
|-----|--|-----|----|
| 7.  | Drooping eyelid or eyelids<br>If YES, which is usually affected?<br>right eyelid<br>left eyelid<br>both eyelids  | YES | NO |
| 8.  | Congested nostril or nostrils<br>If YES, which is usually affected?<br>right nostril<br>left nostril<br>both nostrils  | YES | NO |
| 9.  | Is the pupil of one eye ever noticeably smaller than the pupil of the other eye<br>If YES, which is usually affected?<br>right pupil<br>left pupil<br>either pupil           | YES | NO |
| 10. | Diplopia (seeing double)   | YES | NO |
| 11. | Paresthesia (peculiar sensation e.g. tingling or burning or a distorted or wrongly localized sensation)<br>If YES, please give details _____                                 | YES | NO |
| 12. | Paresis (slight or incomplete paralysis)<br>If YES, please give details _____<br>_____   | YES | NO |
| 13. | Numbness<br>If YES, please give details _____  | YES | NO |
| 14. | Slurred speech   | YES | NO |
| 15. | Dysphasia (difficulty with language e.g. difficulty in choosing the correct word or phrase, problems in co-ordinating words, failure to arrange words in their proper order. | YES | NO |
| 16. | Feeling of weakness  | YES | NO |
| 17. | Trembling  | YES | NO |
| 18. | Ataxia (loss of co-ordination of movement so one is "clumsy")  |     |    |
| 19. | Faintness  | YES | NO |

- |     |   |     |    |
|-----|---|-----|----|
| 20. | During a headache have you ever lost consciousness  | YES | NO |
| 21. | Alterations in mood or outlook (e.g. Irritability or tension, depression, feeling of exaggerated well-being, uncommon energy or vigour, excitability, talkativeness).<br>If YES, please give details _____<br>_____ | YES | NO |
| 22. | Unusual hunger, desire for snacks etc.  | YES | NO |
| 23. | Attacks of nausea   | YES | NO |
| 24. | Attacks of vomiting   | YES | NO |
| 25. | Excessive yawning   | YES | NO |
| 26. | Pains in neck or shoulders  | YES | NO |
| 27. | Blotchy patches on skin or rashes   | YES | NO |
| 28. | Unusual pallor  | YES | NO |
| 29. | Noticeable increase in weight over a short time   | YES | NO |
| 30. | Swelling of fingers, waist or breasts   | YES | NO |
| 31. | Increase in frequency of volume of urination at the time the headache eases.  | YES | NO |
| 32. | Do you have any other symptoms associated with your headaches<br>If YES, please give details _____<br>_____   | YES | NO |

---

---

SECTION 2

IF YOU HAVE HAD A HEADACHE DURING THE PAST YEAR PLEASE ANSWER ALL THE QUESTIONS BELOW FOR YOUR HEADACHES DURING THE PAST YEAR ONLY; WE DO NOT WANT DETAILS OF ANY HEADACHES THAT HAPPENED MORE THAN ONE YEAR AGO UNLESS SPECIALLY MENTIONED.

IF YOU HAVE NOT HAD A HEADACHE DURING THE PAST YEAR, PLEASE TURN TO THE END.

- |    |  |     |    |
|----|--|-----|----|
| 1. | Do you remember your headaches starting at any particular age? | YES | NO |
|    | If YES, how old were you? _____                                |     |    |
-

2. Do your headaches usually begin at the same time of day? YES NO

If YES, please give details \_\_\_\_\_

3. Do any of the following "bring on" or give you headaches? Please tick any that do.

Anxiety

Worry

Emotion

Depression

Shock

Excitement

Release from tension or from worry

Over-exertion

Lack of sleep

Physical or mental fatigue

Bending or stooping, as in gardening

Lifting heavy weights or straining of any sort

Change of routine e.g. holidays, shift-work, or change of job

Late rising, especially at weekends or on holiday

Travel

Change of climate

High winds

Bright sunlight, bright artificial light or glare of any kind;

Flourescent light

Flashing or flickering light

Prolonged focusing on T.V. or cinema screen

Very hot baths

Noise, particularly loud and high pitched sounds

Intense odours or penetrating smells

Use of sleeping tablets

Alcohol

High blood pressure

Prolonged lack of food - fasting or dieting

Continued use of oral contraceptives

Toothache and other local pains in head or neck

Certain foods e.g. fried foods, chocolate, citrus fruits

pastry, onions

If certain foods give you headaches, please list them

\_\_\_\_\_

4. Do any of the following lessen or get rid of your headaches?

Darkness

Resting lying down



Resting sitting up  
Making yourself relax  
Alcohol  
Holidays

Are there any other things which lessen or relieve your headaches? YES NO  
If YES, please give details \_\_\_\_\_

---

5. Do you take any drugs to lessen or get rid of your headaches? YES NO

If YES, please complete the table below for all the drugs  
you take

Name of drug	Dosage usually taken

Have you had any other treatment for your headaches? YES NO

If YES, please give details \_\_\_\_\_

---

SECTION 3

IF YOU ARE FEMALE PLEASE ANSWER THIS SECTION

IF YOU ARE MALE PLEASE TURN TO THE END

1. Have your periods started? YES NO Please  
If NO, please turn to the end tick  
If YES, at what age did your periods start? correct  
answer

2. Have you reached the menopause (i.e. if you are not pregnant  
and yet have not had a period in the last 6 months) YES NO

If NO, do you have a regular monthly cycle?  
(For the monthly cycle count the first day of bleeding  
as Day One and count the day before the next lot of  
bleeding as the last day)

On average how many days does the cycle last?  
\_\_\_\_\_

If YES, did you have a regular monthly cycle?  
(see above for definition of monthly cycle)

YES NO

On average how many days did your monthly cycle last? -----

	OFTEN	SOME-TIMES	NO
3. Have you ever had any of the following symptoms associated with your periods?			
1. Pre-menstrual tension (i.e. depression, irritability, lethargy and tension during the ten days before the period starts.			
2. Breast tenderness			
3. Severe pain before the period starts			
4. Severe pain during the period.			
5. Severe pain after the period finishes			
6. Pain half-way between periods (Mittelschmerz)			
7. Do you gain a lot of weight just before a period and lose it during the period (water loading)			

4. Are you TAKING any form of 'the pill' or other treatment with female hormones?

If YES, please give the name -----

How long have you been having this particular treatment?

From ----- month ----- year

YES NO Please tick correct answer

5. Have you EVER TAKEN any form of 'the pill' or other treatment with female hormones?

If YES, please give details below

Name of tablets	Taken from (mth. yr.)	Taken until (mth. yr.)

YES NO Please tick correct answer

6. If you have headaches are they associated with any particular stage of your monthly cycle

If YES, please give details -----

YES NO

PLEASE RETURN THE QUESTIONNAIRE TO:-

Miss L.M. Debney,  
Neuropsychology Unit,  
Applied Psychology,  
University of Aston,  
Gosta Green,  
Birmingham, B4 7ET.

## FLICKER QUESTIONNAIRE

### SOME QUESTIONS ABOUT HOW GLARE, FLICKER AND OTHER VISUAL STIMULI IN THE ENVIRONMENT AFFECT YOU

NB: (Points to be made to the subject at the start of the structured interview).

Different people find different things a problem. We do not expect you to find all of the following distressing to look at and likely to bring on a migraine. Please answer all the questions. Your answers, along with those of other migraine sufferers will help us to assess what are the major migraine provoking aspects and may bring out points we have missed. Please add any extra comments you may wish.

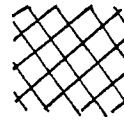
- 1a. Many people enjoy watching films at the cinema. Do you, or did you, go to the cinema much?
- b. Do you, or did you, find watching films at the cinema, pleasant or likely to bring on a headache?
- 2a. Many people watch television. Do you have a television?
- b. About how much television do you watch (e.g. 2 or 3 hours a day; 6 hours per week; 6 hours a day)?
- c. Does watching television ever cause you discomfort or bring on a headache? (Please give details).
- d. If television can cause you discomfort or bring on headaches, do black and white or colour televisions cause you the most trouble when watching, or is there no difference, or have you not had the chance to compare?
- e. Any other comments?
- 3a. Do you drive?
- b. If you drive, about how much driving do you do (e.g. short journeys for shopping each week and some long ones when going on holiday)?

- c. If you drive, do you do any night driving?
  - d. While driving (or being driven) during the day, do you notice any situations, in particular those associated with glare or flicker, that you find distressing and/or likely to cause a migraine?
  - e. While driving (or being driven) at night, do you notice any situations, in particular those associated with glare or flicker, that you find distressing and/or likely to cause a migraine?
  - f. Some cities have roads passing under other roads through tunnels or underpasses. Have you ever been through any? Some migraine sufferers have commented on the lighting used in these, and say some forms of lighting cause them distress while others do not and are quite comfortable. If you have been through any underpasses have you any comments on the lighting?
  - g. Do you find you are a "better traveller" (i.e. fewer headaches, sickness, etc.) when travelling by train, coach or car?
  - h. Any other comments?
- 4a. Lighting is another big area we are interested in. What sort of lighting do you have in your house (e.g. fluorescent tubes; bright bulbs; dim bulb, wall lighting; dimmer switches, etc.) and which do you prefer, and why?
- b. Any comments about lighting in other places, e.g. shops, offices, supermarkets, etc.?
- 5a. A proportion of migraine sufferers complain that looking at certain colours for a while can "bring on" their attacks, e.g. "I was trying to make a (colour) dress for my daughter", said one woman, "but if I did more than 15 minutes on it I got a bad 'migraine'". She had found the same effect sitting in rooms decorated mainly in this colour.
- Is this one of your problems? If so, which colour or colours affect you and could you give examples of when you have noticed the effect?
- 6a. Similarly, some people are affected by patterns, e.g. on wall-paper. Overleaf are a few examples of patterns. Do any of these or any others affect you or are patterns not a problem for you? You may add any extra comments you wish.

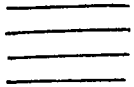
Some Patterns:



vertical stripes



diagonal grid



horizontal strips



concentric stars



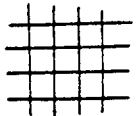
swirl



polka dots



checkerboard



grid

Please answer below:

7. Any other situations involving glare or flicker that cause you problems?

### A.5.1 WORDING OF EXPLANATORY LEAFLET ON ELECTROENCEPHALOGRAMS

E.E.G. stands for ELECTROENCEPHALOGRAM.

The E.E.G. is a recording of the very small electrical changes which occur in the brain all the time. These are picked up by a set of silver discs which are placed on the scalp after making small partings in the hair. This is why we ask subjects to come for their E.E.G. with clean hair, entirely free from grease, cream or lacquer.

This is not a treatment; the test is as harmless as having a photograph taken. There is no sensation, and it has no effect on you during, or after, the recording.

The whole procedure takes about 2 hours so it is important for you to arrive on time for your appointment.

NEUROPSYCHOLOGY UNIT  
APPLIED PSYCHOLOGY DEPARTMENT  
UNIVERSITY OF ASTON

A.5.2 COVERING LETTER OR INSTRUCTION SHEET FOR PATIENTS GIVEN AT INITIAL INTERVIEW

This sheet was handwritten during the interview while the patient completed HQ1. By doing this and assembling the rest of the items to give to the patient it was hoped the patient would feel able to answer the questionnaire at their own speed and not feel pressurized.

The reasons for these instructions are given in the text of Section 2.6.

The text of the instruction sheet was as follows:

University telephone number and extension

MISS LORNA DEBNEY

When you come would you please

1. Bring a list of the drugs you have taken in the ten days before the test (see below).
2. Bring your Migraine Chart.
3. Bring your glasses if you have been prescribed any.
4. Bring your migraine drugs.
5. Have something to eat before you come.
6. Complete the questionnaire as far as possible and bring it with you.

N.B. Do not go to any great lengths to find out all your relatives' illnesses, just fill in what you know.

DRUGS TAKEN

Day 1

Day 2

Day 3

Day 4

Day 5

Day 6

Day 7

Day 8

Day 9

Day 10

Test Day



A.3.3 LETTER ADDRESSED TO HEADS OF THE ADULT INSTITUTES FOR  
FURTHER EDUCATION

This letter was sent out on headed notepaper and the letter read as follows:

Dear

The Neuropsychology Unit, in co-operation with the Migraine Clinic at the Birmingham Eye Hospital and the British Migraine Association has been carrying out some research into headaches and migraine. A large number of people with severe migraine have already been investigated.

We are now looking for some volunteers (who would be paid) to help us with this research by providing a normative sample. Obviously the investigation will have to be the same as that used on the migraine patients. Each person would complete a questionnaire on their general health and the frequency of any headaches which they have. They would be asked to carry out some simple visual tests and an EEG recording would be performed. An explanatory leaflet, giving details of the EEG recording, is enclosed.

Since our normative sample will need to be age matched to the patients, we wondered whether it would be possible for you to contact your adult education students who might be willing to help us. I enclose a number of sample notices which I would be grateful if you could display in your adult education centre, or otherwise brought to your students' attention.

If you have any queries whatsoever my staff or I would be most willing to answer them, or to let you observe investigations being carried out. If you are able to co-operate with us on this project, I would be grateful if you would let me know. A stamped addressed envelope is enclosed for your reply.

Yours sincerely,

Dr. G. F. A. Harding  
Reader in Neuropsychology  
Honorary Consultant Neuropsychologist  
Birmingham Area Health Authority (Teaching)

# Adult Education Students

Would you like to help research into headaches and earn some extra money?

Headaches make a misery of many people's lives, and the University of Aston with the Birmingham Migraine Clinic are studying many sufferers from severe migraine. We urgently need to compare our findings with those from people of similar ages (between 20 and 70) who do not get migraine (but may have other sorts of headaches).

Volunteers, who will each be paid £2.00 are asked to answer some questions on general health, do a few simple visual tests and have an EEG recording. All results are treated as confidential.

An EEG is a recording of the very small electrical changes which occur in the brain all the time. These are picked up by a set of silver discs which are placed on the scalp after making small partings in the hair. This is not a treatment; the test is as harmless as having a photograph taken. There is no sensation, and it has no effect on you, during, or after the recording. We make the visits enjoyable and interesting for our subjects.

Car parking facilities will be available and appointments made in the mornings, afternoons or evenings.

Please Help Us and Migraine Sufferers!!

Simply enclose a slip giving:

Name	Date of Birth
Address	
Telephone No.	

In the pre-paid envelope provided, to "Migraine Research, Neuropsychology Unit, Applied Psychology Dept., University of Aston, Birmingham B4 7ET."

A.3.4 LETTER SENT TO CONTROL SUBJECTS WHO WERE CONTACTED  
ORIGINALLY BY 'PHONE TO TRY AND ARRANGE AN APPOINTMENT  
AT SHORT NOTICE

The final sentence in the third paragraph would have a section deleted as appropriate. The letter was on headed paper and the text read as follows:

Dear

I have made you an appointment to come and help with the research into Migraine Headaches on .....  
at .....

I enclose a map showing how to find the Neuropsychology Unit and the Visitors Car Park (for which I enclose a ticket).

I also enclose two questionnaires. Both of these are filled in by the patients from the Migraine Clinic to provide necessary clinical details. Could you please complete both so that we may make a proper comparison (if you are not sure what is meant by a question then put a ring round the question number and we can sort it out when you come). Could you please return the questionnaires in the stamped addressed envelope provided/bring the questionnaires with you.

When you come for the appointment could you (1) bring your glasses with you if you have been prescribed any, and (2) could you also have something to eat before you come.

I look forward to seeing you and will be happy to explain the work we are doing here.

With many thanks for your help.

Lorna M. Debney M.Sc. (Miss)

A.3.5 LETTER SENT TO CONTROL SUBJECTS WHO WERE NOT CONTACTED  
ORIGINALLY BY 'PHONE AND AN EXAMPLE OF THE FORMAT FOR  
APPOINTMENT TIME CHOICE SHEET

The letter was on headed paper and the text read as follows:

Dear

Thank you for offering to take part in the research on Headaches.

It would greatly help us if you could complete and return both:

1. The sheet showing which times we have available on which we would like you to indicate times when you could come.
2. The two questionnaires. Both of these are filled in by the patients from the Migraine Clinic to provide necessary clinical details. Could you please complete both so that a proper comparison may be made.  
If you are not sure what is meant by a question then put a ring round the question number and we can sort it out when you come.

A stamped addressed envelope is provided for your reply.

I look forward to seeing you and will be happy to explain the work we are doing here.

With many thanks.

Yours sincerely,

Lorna M. Debney, M.Sc. (Miss)

An example of the type of format used for the time choice sheet:-

TIME-CHOICE SHEET

The Neuropsychology Unit works part of the time as a diagnostic clinic for the West Midlands Regional Health Authority and part of the time does teaching and research. The times which are definitely available for the Migraine Research are therefore limited. The times which are definitely available are listed below, and we ask you to indicate which are convenient (see below). We also ask you to indicate if any other mornings or afternoons in the week would be suitable as should any clinic sessions be cancelled or otherwise not booked, we would then be able to use such sessions.

Name .....

(A) TIMES WE HAVE DEFINITELY AVAILABLE

Could you a) Cross out those which will be inconvenient for you  
i.e.



b) If you wish to indicate which of the times you might  
be able to come would be most convenient for you,  
would you either

i) tick these, i.e.



or ii) if you wish to indicate order of preference,  
could you number the most convenient times  
"1", the next most convenient times "2" and  
so on.

I) FRIDAY MORNINGS

Time	May			June			
	14	21	28	4	11	18	25
9.00	<input checked="" type="checkbox"/>			<input checked="" type="checkbox"/>			
11.30	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>					

2) EVENINGS

Generally the evenings are free from 5.00 pm onwards. The whole  
procedure takes about 2 hours so on those evenings which are  
possible for you, could you please put down what time you could  
arrive, i.e. to arrive any time from 5.00 pm to 7.30 pm. Those  
evenings marked \* are available from 7.30 pm only.

MONTH	Monday	Tuesday	Wednesday	Thursday	Friday
May	3 <input checked="" type="checkbox"/>	4 <input checked="" type="checkbox"/>	5	6 <input checked="" type="checkbox"/>	7
	10*	11*	12 <input checked="" type="checkbox"/>	13*	14 <input checked="" type="checkbox"/>
	17	18	19	20*	21
	24	25	26	27*	28
	31	1	2	3*	4
June	7	8	9 <input checked="" type="checkbox"/>	10*	11
	14	15	16	17*	18
	21	22	23	24*	25

(B) OTHER TIMES CONVENIENT FOR YOU

Should any clinics be cancelled for any reason, we would like to be able to use the time, if it is convenient, for our volunteer subjects. Please indicate if any mornings (other than Friday mornings which are listed above), or any afternoons would be convenient for you to come, e.g. Monday mornings. Please give any time restrictions that would affect you, e.g. Monday mornings after 10.00 a.m.

Note Before the time-choice sheet was sent out those times already booked were marked with an "X" as illustrated.

A.3.6 APPOINTMENT LETTER TO CONTROL SUBJECTS CONTACTED BY LETTER  
(SEE A.3.5)

This letter was on headed paper with the text as follows:

Dear

I have made you an appointment to come and help with the research into Migraine Headaches on .....  
at ..... Please post to us the enclosed reply-paid card to let us know you can come.

I enclose a map showing how to find the Neuropsychology Unit and the Visitors Car Park (for which I enclose a ticket).

When you come for the appointment would you (1) bring your glasses with you if you have been prescribed any, and (2) could you also have something to eat before you come.

I look forward to seeing you and will be happy to explain the work we are doing here.

With many thanks for your help.

A.5.7 TEXT OF THE COVERING LETTER SENT OUT INITIALLY WITH HQ1 TO  
A SAMPLE OF FIRST YEAR U.K. UNDERGRADUATES.

The letter was on headed paper and the text read as follows:

Dear

Many people suffer from headaches either intermittently or very frequently and these can make life a misery. People who are headache free as well as those who suffer are important in my Ph.D. research project which aims to improve understanding of headaches, their causes, diagnosis and possible cures. It would greatly help this research if you would complete the enclosed questionnaire (approved by University Authorities and the Guild of Students). It should be emphasised that all information is treated as confidential. Please complete the questionnaire whether or not you suffer from headaches, and return it in the stamped addressed envelope provided.

We are also anxious to obtain a number of volunteers, over the next twelve months to take part in a further study. From among those willing to volunteer, I would like to select subjects for further study on the basis of the questionnaire responses. These subjects will include the headache free, those with mild headaches, those with severe ones, those who have other symptoms associated with their headaches (as in some forms of migraine) and those who do not. These subjects will be paid at the rate of 50p per hour and could expect to earn in the region of £1.50 to £2.00. This further study is basically an EEG (see enclosed slip) a further questionnaire and simple visual tests. Again, all information is treated as confidential. It should be noted that these tests will be arranged to suit the convenience of the subject, on mornings, afternoons or early evenings. Please indicate on the tear-off slip below whether you are willing to take part in the further study and return the slip, with the completed questionnaire, in the stamped addressed envelope.

Many thanks for your co-operation.

Miss Lorna M. Debney

cut here \_\_\_\_\_ cut here

Please delete as applicable

I am/am not willing to take part in the further study

NAME (Block Capitals) .....

Signed .....

Address for Correspondence (Block Capitals)

.....

.....



A.3.8 LETTER SENT IN THE SUMMER TERM TO VOLUNTEER STUDENT SUBJECTS  
ASKING THEM TO MAKE AN APPOINTMENT FOR THE ELECTRO-  
PHYSIOLOGICAL STUDY

Headed paper was used and the text read as given below. An example of the time-choice sheet referred to is given in A.3.5.

Dear

Thank you for returning the Headache Questionnaire, and for volunteering to help in the research. I would very much like you to come along for the further tests, for which payment will be made. You may expect to earn £1.25.

I realise that you will be busy with exams this term, but since exam dates vary considerably I am hoping some people will be able to come before their exams, and others after their exams are over.

Due to the large number of projects being carried out in the Unit at the moment, the times I have to offer are limited. The times definitely available are shown on the enclosed "time choice sheet". If these are inconvenient it may be possible to arrange an alternative time, this would require you visiting me at the Unit so that I could arrange to borrow the time from whoever normally has that session. The Unit is on the second floor of College House, (entrance between Lloyds Bank and the Bookshop), turn left at the top of the stairs.

Please note that the enclosed "time choice sheet" extends beyond the end of the term, this is because it is also sent to people outside the University who are helping with a different series of tests which are also to do with the research into Headaches.

Please complete the enclosed "time choice sheet" and return it in the stamped addressed envelope provided, I will write to confirm the appointment time.

With many thanks.

Yours sincerely,

Lorna M. Debney M.Sc. (Miss)

A.3.9 FOLLOW-UP LETTER TO THOSE STUDENTS WHO FAILED TO COMPLETE  
AND RETURN HQ1 ON THE FIRST REQUEST

The letter was on headed paper and the text read as follows:

Dear

Last year I sent you a letter and a questionnaire as part of some research into headaches. I did not receive a completed questionnaire from you. It is important to this research that as many people as possible return completed questionnaires. So far over 60% have returned completed questionnaires, please help to make this 100%.

People who are headache free as well as those who suffer headaches are important to this research, which aims to improve understanding of headaches. All information is treated as strictly confidential.

Please complete the questionnaire (approved by University Authorities and the Guild of Students), whether or not you suffer from headaches, and return it in the stamped addressed envelope provided.

In addition to the questionnaire, we are running a further study with the help of paid volunteer subjects, at times to suit each volunteer, on mornings, afternoons or early evenings. From these volunteers, subjects for the further study are selected on the basis of the questionnaire responses. These subjects include the headache-free, as well as those with headaches of different types, with different symptoms. These subjects earn £1.25 over a two hour period.

This further study is basically an EEG (see enclosed slip), a further questionnaire, and simple visual tests. Again, all information is treated as confidential.

Please indicate on the tear-off slip below whether you are willing to take part in the further study and return the slip, with the completed questionnaire in the stamped addressed envelope.

Many thanks for your co-operation.

Lorna M. Debney M.Sc. (Miss)

cut here \_\_\_\_\_ cut here

Please complete and return with completed questionnaire.

I am/am not willing to take part in the further study (delete as applicable)

NAME (Block Capitals) .....

Signed .....

Address for Correspondence (Block Capitals) .....

.....

.....

A.5.10 LETTER SENT TO VOLUNTEER STUDENT SUBJECTS ASKING THEM TO  
MAKE AN APPOINTMENT FOR THE ELECTRO-PHYSIOLOGICAL STUDY

Headed paper was used and the text read as given below. An example of the time-choice sheet referred to is given in A.5.5.

Dear

Thank you for returning the Headache Questionnaire which I sent you last year, and for volunteering to help in the research. I would very much like you to come along for the further tests, for which payment of 50p an hour will be made, either this term or next.

Due to the large number of projects being carried out in the Unit at the moment the times I have to offer at present are limited to two sessions of Friday morning (9.30 am - 11.30 am and 11.30 am - 1.30 pm), to early evenings Monday to Friday (any two hours between 5.00 pm and 8.00 pm) and Saturdays (11.00 am - 1.00 pm and 2.00 pm - 4.00 pm).

If these are inconvenient it may be possible to arrange an alternative time, this would require you visiting me at the Unit so that I could arrange to "borrow" the time from whoever normally has that session. The Unit is on the second floor of College House, entrance between Hudsons Bookshop and Lloyds Bank, turn left at the top of the stairs.

If you could complete the attached sheet and return it in the stamped addressed envelope provided, I will write to confirm the appointment time.

With many thanks.

Yours sincerely,

Miss Lorna M. Debney, M.Sc.

#### APPENDIX 4

Multiscale overlay for manual analysis of photic driving. This was made by:

- (a) setting up the laboratory as for a subject recording
- (b) obtaining the EEG pen write-out of the stroboscope output at various rates of flash
- (c) mounting a sample of each flash rate recorded on a sheet
- (d) producing transparent copies with a Thermo-Fax Copying Machine (Minnesota Mining and Manufacturing Co., Ltd.).

This method ensured as far as possible that the overlay would correspond to the EEG recordings to be assessed, insofar as the factors of EEG machine characteristics (including machine speed), and stroboscope characteristics would be the same for both the records and the overlay.

